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ADRENAL-SYMPATHETIC SYNDROME

CHROMAFFIN TISSUE TUMOUR WITH PAROXYSMAL HYPERTENSION

BY

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From St. James' Hospital, London

Received May 21, 1943

The chromaffin cells of the adrenal medulla are a part of the scattered "chromaffin tissue system." The tumours of these cells, the pheochromocytomata or adrenal paragangliomata are nearly always benign, but usually produce paroxysmal hypertension ending fatally if the tumour is not removed.

There are reports of 152 cases of pheochromocytoma. The only extra-adrenal paragangliomata that have produced the hypertensive picture are those arising in the retroperitoneal tissues between the kidneys: of 13 such cases, 9 had the cardiovascular syndrome typical of the adrenal cases, and they form part of one clinical problem and are considered with the adrenal cases here. Of these 165 cases, 90 have been described since 1929, and 36 operations have been reported.

Paragangliomata arising from the intrathoracic sympathetic chain, from below the bifurcation of the aorta, from the coccygeal body, from the carotid body, and in the wall of the intestine are described, but very few of these are true tumours of the chromaffin tissue system (Da Costa, 1939-40; Christic, 1933) and none has given the cardiovascular picture.

In 1886 Frankel reported an autopsy finding of bilateral adrenal tumours and cardiac hypertrophy in a girl of 18 who for three years had had attacks of palpitation, headaches, and vomiting. The first full clinical description was by Labbé, Tinel, and Doumer (1922) who observed the paroxysmal hypertension in the attacks. The first case in which the correct diagnosis was made and followed by operation and cure was that of Pincoffs and Shipley (1929).

The final important step was by Beer, King, and Prinzmetal (1937) who showed that during the crises the blood contained large amounts of adrenaline.

Incidence and pathological anatomy. The incidence of pheochromocytoma in men and women is equal. Cases with the cardiovascular syndrome occur at all ages; mostly between 20 and 50 years. The association with generalized neurofibromatosis is recorded in nine cases.

The common lesion is a benign adenoma of one adrenal body. Sixteen bilateral tumours are recorded: of these, 8 showed a cardiovascular syndrome and 6 were malignant. Malignant pheochromocytomata are rare (15 cases), but may show a hypertensive picture. In about one case in ten the tumour is extra-adrenal, lying between the adrenal and the midline.

In size the tumour is usually like an orange, but tumours weighing from 13 to 2000 grams are described. The surface is often bossy and a line of remnants of cortical tissue is common. On section there are usually hæmorrhagic cysts set in fibrous tissue.

Histology. (See Geschickter (1935) for good illustrations and Edwards (1937) and van Goidsenhoven and Appelman (1934) for methods of staining.) The commonest picture is of polyhedral cells of notably varied size and shape arranged in alveolar masses separated by fibrous septa, resembling cirrhotic liver with hyperplasia. The abundant cytoplasm is finely granular and the nucleus round or oval with a single nucleolus. Multinucleated giant cells and syncytial sheets of cells are sometimes seen. Occasionally there are groups of cells resembling lymphocytes. The cells may be arranged round vascular spaces giving pseudo-rosettes (Peyron, 1930).

In tissues fixed with chrome salts the characteristic chromaffin reaction is seen. The brown granules may be seen in the cytoplasm or nucleus, or in the stroma.

Adrenaline in tumours. That these tumours give strongly positive reactions to chemical tests for adrenaline (Edwards, 1937) was shown thirty years ago. These results have now been confirmed by demonstrations of a pressor principle behaving like adrenaline. The quantitative estimations vary from 0.12 up to 20 mg. (Belt and Powell, 1934) per gram of tumour tissue (normal adrenal medulla about 0.4 mg.).

Association of other adrenal body tumours with hypertension. Paroxysmal hypertension has been reported with adrenal ganglioneuroma (Rogers, 1933), with neuroblastoma (Ernoult and Picard, 1934) and with cortical tumours (Rimbaud and Delmas, 1939; Plazy and Germain, 1932). Persistent hypertension has been found with retroperitoneal ganglioneuroma (Jergensen, 1933), with an adrenal

"sympatheticoblastoma" (Binger and Craig, 1938) and is, of course, not uncommon with adrenal cortical tumours.

Two cases are here reported, one fully and one more shortly, and this is followed by a general discussion of the clinical picture, diagnosis, and treatment.

REPORTS OF TWO CASES

An aircraftman, aged 29, awoke one morning with profuse sweating, pain across the epigastrium, and vomiting. These continued and on the third day he felt very ill and was sent to hospital. There was no palpitation. He had never had any illness like this before.

On admission he was in a state of collapse. The extremities were blue and cold. His mouth temperature was normal. The pulse was 80, tiny, but hard; the blood pressure, 197/167. No signs of disease were detected in the heart or lungs. There was herpes febrilis of the lip and vague tenderness of the right side of the abdomen. The urine showed a trace of albumen.

He was treated with warmth, rest, morphine, and fluids by mouth. There was no further vomiting and he improved steadily. Next day he felt and looked much better; the following day the blood pressure was 125/100, and a provisional diagnosis of paroxysmal hypertension from adrenal medullary tumour was made.

Previous history. The family history was of no significance. Up to 25 years of age he was healthy save for insomnia at times and, at 22, a right-sided orchitis, which left the testicle atrophic.

From the summer of 1937, that is, for four years, nearly every morning shortly after getting up, he had a few minutes' nausea, usually accompanied by palpitation, but without vomiting. After this nausea passed off he felt weak for 10 to 15 minutes.

In July, 1938, he had an attack of thumping of the heart—the rate and rhythm being unaffected. Later that summer for half one day he felt ill and for a week after had severe headache and felt weak.

From November, 1938, to April, 1939, he had severe headaches. Three weeks after they started he began to have attacks of thumping of the heart during which the headache was worse. He was in St. Thomas's Hospital in December, 1938, and while in bed there the palpitation recurred frequently, the forcible beat of the heart being visible from several feet away. No signs of organic disease were found, except that the blood pressure was 144/100. The palpitations continued for a time sometimes accompanied by choking feelings and vomiting. After they ceased the headaches gradually cleared up.

At the end of 1939 and occasionally since he noticed that sometimes when leaning to the left he would suddenly feel nervous and dizzy.

In July, 1940, he joined the R.A.F. Sometimes, during the next winter, he had a momentary feeling of intense weakness in the legs while walking. In February, 1941, at a medical examination for aircrew he says that his blood pressure seemed to arouse interest; at a re-examination it was 120/70 and he was passed.

During the summer of 1941 on several occasions at drill he was told he was pale. Only sometimes was this pallor accompanied by subjective feelings of trembling, anxiety, and faintness, lasting up to half a minute. Later these sensations occurred about twice a day and he also noticed that crouching would bring them on.

In July, 1941, the severe paroxysm described led to his admission to hospital. While there he had some further minor crises which may be conveniently described here.

One afternoon he was observed to be pale. He said he felt well but had just been passing water which since cystoscopy, for which a meatotomy had been needed, had been painful. His blood pressure was found to be 210/135; ten minutes later it was 150/105 (at rest at this time it varied from 120/95 to 130/110). This was evidently a symptomless paroxysm of hypertension induced by painful micturition. Similar attacks were observed on succeeding days.

During the perirenal pneumography a second insufflation gave severe pain. He became very distressed, complaining of suffocation; his face was congested and his blood pressure was 240/170. This attack lasted about ten minutes and was followed by prostration for half an hour.

Progress in hospital and investigations. Two days after admission he looked and felt well. For the next two weeks, however, he had a symptomless pyrexia, often from 99 to 100.6° F., for which no cause could be found.

Psychologically the patient was a placid, well-balanced person without conscious anxiety feelings and of normal sexuality.

X-ray of the chest showed no disease of heart or lungs, but a dextrocardia with transposition of viscera was revealed. The teeth were healthy. The blood two days after admission showed R.B.C., 5.0 million; Hb. 98 per cent (Haldane); W.B.C., 21,200 (neutrophils 82 per cent, lymphocytes 11 per cent, monocytes 7 per cent), and eleven days later Hb. 85 per cent, W.B.C. 8000 (neutrophils 75 per cent). Blood chemistry (20/9/41) gave serum chloride as sodium chloride 560 (normal 560–

620), sodium 326 (normal 325–350), potassium 46 (normal 16–20) mg. per 100 c.c.—a very significant rise in potassium level.

A rounded tender mass was palpable high up in the left loin. As the pyrexia abated this mass seemed to become less easily felt and less tender. Repeated examinations of the urine revealed only an occasional trace of albumen; its specific gravity ranged from 1024 to 1001 in tests, and the urea clearance was 113 per cent normal. X-ray showed no renal stone, and cystoscopy a normal bladder. Intravenous pyelography showed the left kidney slightly depressed with a little deformity of the upper calyx.

Attempts to induce attacks by the various manœuvres described below were made but none of these affected the blood pressure level. As noted above, for a few days after cystoscopy he had symptomless paroxysms of hypertension induced by the dysuria. These were an important confirmation of the diagnosis. Adrenaline was given intramuscularly. The pressure which was about 160/120 before the injection was little affected by 0.25 c.c. of 1/1000 solution, but after 1.0 c.c. it rose to 205/140 for a few minutes. As the rise began the patient said it was like the beginning of an attack. On another day 1.25 c.c. gave pallor and palpitation but only a slight rise of pressure. A cold pressor test (Hines and Brown, 1933) gave a "positive" result, the pressure rising from 135/100 for 3½ minutes to reach 160/120 with a slower fall.

The electrocardiographic findings are given later (see p. 7).

Operations and progress. Mr. L. R. Broster kindly agreed to operate and it was decided to do an exploratory laparotomy and to remove the tumour by the lumbar route at a second operation.

The evidence obtained from a *perirenal pneumography* by Mr. G. C. Sawyer was too indefinite to help in deciding the side of the tumour. Also, the insufflation on the right side was painful and led to an unpleasant attack.

At an exploratory laparotomy a tumour the size of a tangerine orange was found above the left kidney. The right adrenal body was normal. The blood pressure which before the operation had been rising from 130/108 to 150/112 was after induction 180/120 and remained there throughout, being unaffected by squeezing the tumour. The pulse, 110 and regular at first, soon became irregular in force and after manipulation of the tumour there was an irregular tachycardia (rate 200) for ten minutes. This may have been due to the use of cyclopropane in the presence of excess adrenaline (Burstein *et al.*, 1940). There was no disturbance after the operation and no significant change in the white blood count two days later.

The tumour was removed two weeks later on 24/9/41, under gas-oxygen-ether preceded by omnopon-scopolamine.

For combating the expected fall in blood pressure after removal of the tumour, a 1/100,000 solution of adrenaline HCl in normal saline was prepared. When the patient was anaesthetized a slowly running continuous intravenous drip of normal saline was inserted with provision for switching over to the adrenaline solution if necessary. This drip was kept going during and for some hours after the operation. The tumour was removed through a lumbar incision. The blood pressure, 175/110 at the beginning, rose during the operation to 225/145, and fell to 90/70 in ten minutes after the removal of the tumour. About 10 c.c. of the adrenaline solution restored it to 120/80 for ten minutes, but for some hours after the operation it was about 80/60 and the patient was slightly cyanosed and sweating profusely. The day after it was 140/105, settling on the third day to 130/95. He was given sodium desoxycorticosterone for three days.

He made an uninterrupted recovery and was discharged three weeks later, having had no recurrence of the minor symptoms that were previously of daily occurrence.

When he was discharged, though he was free of infection his white count was still raised, 17,500, neutrophils 78 per cent (the day after the operation it had been 23,000 and 77 per cent). He went to an R.A.F. hospital, and while there he had four minor attacks, and then no further attacks in a year. As the tumour was histologically malignant he was given deep X-ray therapy six months after the operation. He returned to civil life and is working very hard. His weight is well maintained and he writes that he is fit and entirely free of any of the symptoms he had before the operation. This was confirmed by an examination at which his blood pressure was normal.

Description of tumour. The tumour was a flattened ovoid 5.5 × 4.5 × 2.5 cm., weighing 63.5 grams. The surface showed bluish bosses and a line of cortical remnants (Fig. 1). Section showed a fibrous capsule surrounding a matrix which was hard and pearly white in the centre and in which were set round areas of purplish fleshy tissue corresponding to the bosses on the surface (Fig. 2). There were two irregular areas of yellow tissue.

Histology (Dr. H. W. C. Vines). The tumour has a well defined fibrous capsule, into which the tumour cells appear to be infiltrating to some extent. Some lymphatic spaces contain tumour cells.

The tumour is composed of large polyhedral cells, many compressed into spindle cells. There are a few multinuclear cells and some with deeply staining pyknotic nuclei. Mitoses are rare. There are small areas of necrosis with replacement by very loose areolar fibrous tissue; and areas of



FIG. 1.—Case 1. Drawing of tumour, slightly under actual size. The line of cortical remnants and the bosses are visible.



FIG. 2.—Case 1. Section across tumour, slightly under actual size. The fibrous capsule, the fleshy cysts, pearly fibrous matrix, and two areas of yellow fatty tissue are seen.

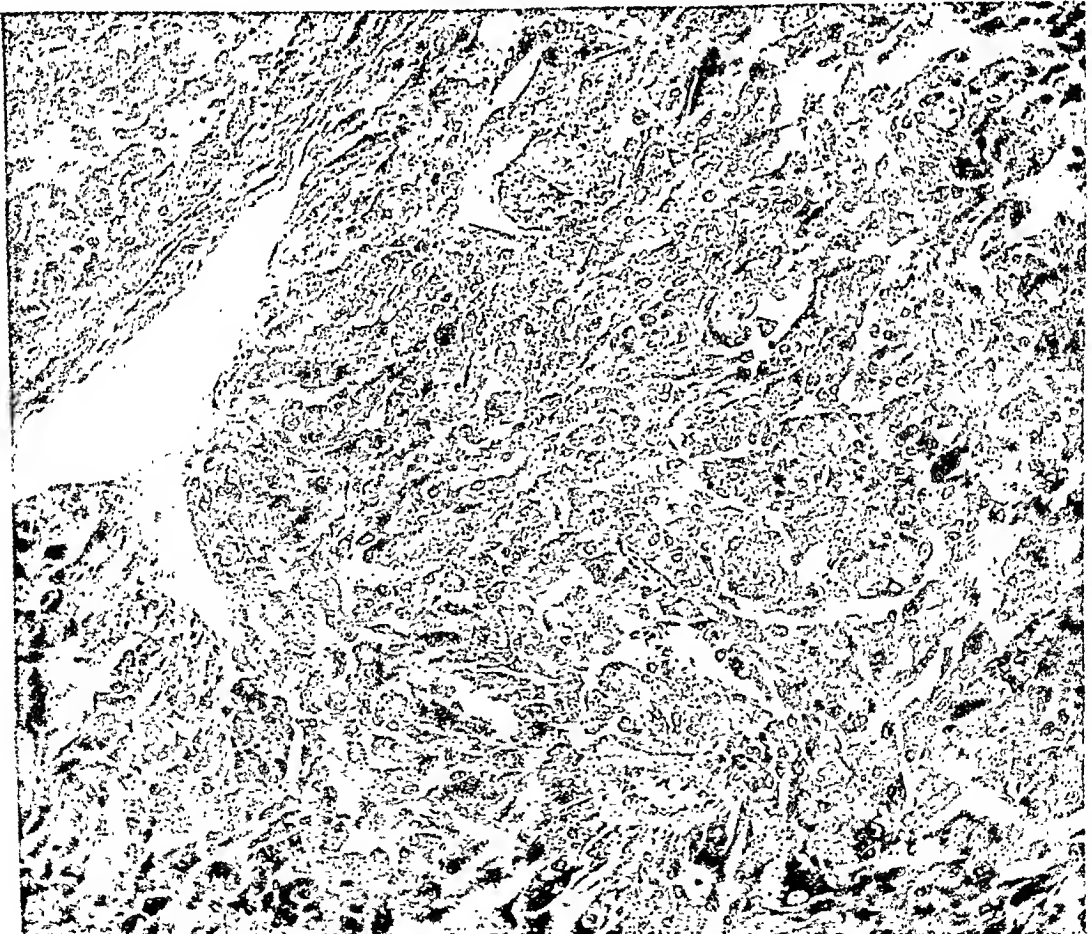


FIG. 3.—Case 1. Microphotograph; $\times 175$; Hx and E. Showing cells of varied shapes and sizes; giant cells visible by the cleft; and at bottom perivascular arrangement of cells.

hæmorrhage. The vessels are numerous and many are thin-walled but not sinusoidal. There is some patchy deposit of hæmosiderin. In some areas perivascular survival of the tumour cells presents the appearance of pseudo-rosettes, or of a papilliferous arrangement. The tumour cells give a chrome reaction (Fig. 4). The growth does not appear entirely benign. It may be called a pheochromoblastoma.

Adrenaline content (Dr. Derek Riechter and Dr. F. C. MacIntosh). This was done on an extract made of a slice across the tumour. By colour reaction with iodine, the adrenaline content was 5.25; and by biological test on atropinized eviscerated cat, 8 mg. per gram of wet tumour tissue (normal adrenal content 0.4 mg. adrenaline per gram.).

Case 2. Short notes of a case which came to my notice during the preparation of this paper, are included. A clerk, aged 25, was invalidated out of the Army in 1940 for "heart trouble." He had

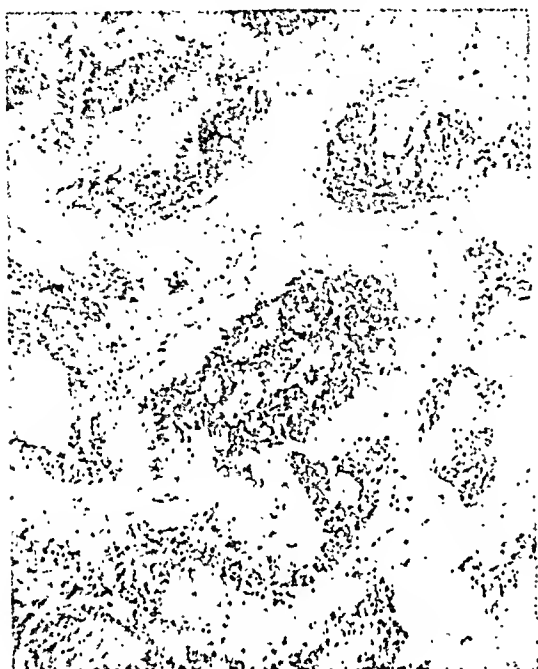


FIG. 4.—Case 1. Microphotograph, chrome-fixed and unstained showing "lobules" of chromaffin cells set in fibrous stroma. Magnification $\times 62$.

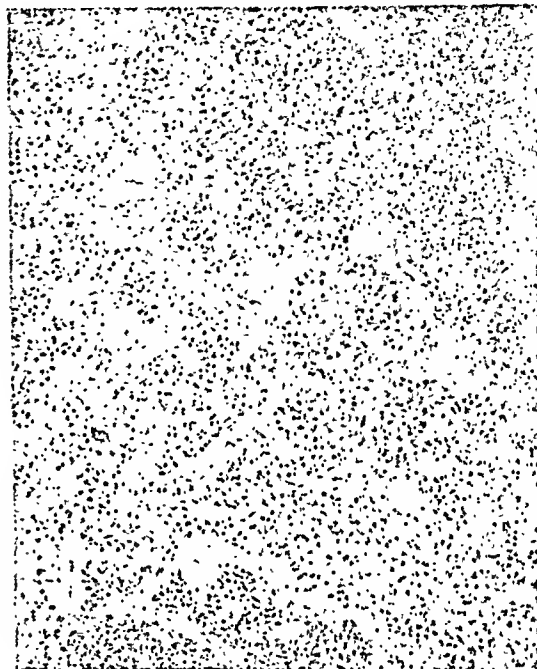


FIG. 5.—Case 2. Microphotograph (Hx and E), showing "lobules" of cells in fibrous stroma. Magnification $\times 66$.

been breathless on exertion, with a few attacks of nocturnal dyspnea. There was no history of nephritis.

One night he developed severe breathlessness. His doctor gave him morphia and sent him to hospital. On arrival he was very cyanosed with audible bubbling respiration and was bringing up a blood-stained froth. There was no overfilling of the veins and no œdema of the ankles. In the chest many crepitations and bubbling noises were heard. His blood pressure was 160/120. The blood urea was 40. He was given oxygen, atropine, and later morphia, but he failed to improve and died nine hours after admission.

At autopsy, both lungs were grossly congested. The heart was of average size, the right auricle dilated, the left of normal size; the mitral valve admitted three fingers. The vessels were normal. The liver showed acute congestion only; the kidneys and the other organs were normal excepting the right adrenal body. This was rounded and enlarged, about 2 inches in diameter. On section there was towards the periphery a large cyst filled with blood and tumour tissue. Histological examination showed normal left adrenal and kidney. The right adrenal showed alveolar masses of polygonal and polymorphic cells in a fibrous stroma (Fig. 5). Chrome staining was not done.

CLINICAL PICTURE

Chromaffin cell tumours of the adrenal medulla may give—(i) Recurrent paroxysms of generalized vasoconstriction accompanied by a remarkable but transient hypertension; the *adrenal sympathetic syndrome*, (ii) Chronic hypertension with renal and cardiac failure, resembling malignant hyper-

tension, (iii) Addison's disease from local pressure on the cortex, an uncommon picture, or (iv) No symptoms. The descriptions given here deal chiefly with the first type which is the commonest, most easily recognized, and most treatable one.

The history of attacks usually extends over several years, even as long as 16 years (Allen, 1940). But they may end fatally after a few months or even days (Edwards, 1937). Sometimes there is a steady progress from mild occasional attacks to frequent and severe ones, but attacks may cease for a time, even for ten years (Hamilton, 1940). At first the blood pressure level is normal between paroxysms, but later these are often superimposed on a persistent hypertension. This may already be present at the earliest examination and occurs in about half the cases of long duration.

The first attack may be severe, but more often the early ones are mild. Or there may have been transient malaise, headaches, nausea, digestive troubles, diverse pains, dizzy spells, palpitations, the significance of which is not realized until a more severe paroxysm occurs. If the condition is not treated these major crises recur. The paroxysms vary in severity and clinical picture but in individual subjects they are often of one type. They may recur irregularly at long intervals, or several times a day, or daily at a set time.

Precipitating factors. Where attacks occur before breakfast, fasting may be a factor, but it is as common for them to occur after meals. Constipation may induce the vascular crises (Foucar, 1939). More easily understood as precipitating causes are exercise and emotion. Pain led to attacks in the present case. Drinking 1500 c.c. of water caused one fatal paroxysm (Howard and Barker, 1937). Attacks occur at operation, even before manipulation of the tumour. By far the commonest precipitating factors are postural, e.g. bending the trunk, combing the hair, etc. Where flexion of the trunk leads to attacks there is usually a palpable tumour, but it is not always flexion to the side of the tumour that provokes them. A steady pressure for two minutes to the adrenal region or to a palpable tumour may induce a paroxysm at once or after a few minutes (MacKenzie and McEachern, 1938). A sharp blow on the abdomen, warming the renal region, pressure on the carotid sinus, and the cold pressor test are other reported methods that may be tried in a suspected case.

But it is to be noted that in half the cases no special precipitating factors have been recorded.

The paroxysms. The recurrent vascular crises are the most important feature of the clinical picture. There is a sudden generalized vasoconstriction producing symptoms and signs from many parts of the body and so causing a characteristic picture. Less commonly patients may complain of symptoms limited to one system, e.g. of recurrent epigastric pain and vomiting or recurrent headache. The accompanying rise of blood pressure shows that it is the symptoms and not the vasoconstriction that is limited in distribution. A more detailed history or examination may yield other evidence of the widespread vasoconstriction. Symptomless paroxysmal rises of blood pressure have been noted by four authors.

Preceding the attack, there may be paraesthesiae or an indefinable malaise which the patient recognizes as the aura of his attack. The commonest first symptom is palpitation, but various feelings in the extremities, epigastric pain, sinking feeling or nausea, substernal constriction or cardiac pain, lusty sneezing (in three cases), throbbing in the temples, dizziness, headache, or a sensation of shakiness or languor may mark the onset of the paroxysm. As it proceeds some or all of these symptoms may develop. A progress of symptoms upwards from the feet is described in several cases, when warmth or tinglings of the feet may be succeeded by cramps in the calves and thighs, then by abdominal colic and epigastric pain with nausea and vomiting, followed by thoracic angina radiating to the arms, then fullness, choking or pain in the neck, throbbing in the temples, dizziness, and finally an atrocious headache. Nausea is described in nearly all attacks and vomiting in most of them; and epigastric discomfort is often noted. Pain in various sites, severe headache, and vertigo are common. Sweating, a sense of hair-pulling (Nuzum and Dalton, 1938), lachrymation, and salivation are symptoms of pharmacological interest. Where the attacks are severe, spitting of blood (from acute pulmonary oedema) may be described. In other cases a condition resembling shock or collapse occurs.

In these major paroxysms the patient is obviously ill. The face is usually pale and anxious, but may be congested or blotchy or may alternate between pallor and redness. Coldness of the extremities is described in nearly every case; usually blanched, the hands may be purplish. A moderate rise of body temperature is common. The pulse is not infrequently noted as being weak or small; in the present case it was tiny but hard. The pulse rate may be up or down and may react differently in different attacks, or variably during one attack. Rhythm irregularities may occur. The heart beat is very forcible and may shake the bed. The second sound at the aortic area is loud and ringing; a transient aortic diastolic murmur may be heard at the height of the paroxysm (Bernal, 1933).

The systolic pressure may rise in a few minutes from 120 to over 300 mm.; and the diastolic in proportion. The level may vary widely during the attack. An initial apnoea or tachypnoea may be seen. An abdominal tumour, not always in the loins, is palpable in about one third of cases; it

may be, in fact, a kidney pushed down by the adrenal tumour. Other common signs are swelling of the neck veins and dilatation of the pupils. During the attack there may be anuria or oliguria with albumen and casts in the urine, and azotæmia, which may exceed 150 mg. urea per 100 c.c. Hyperglycæmia and glycosuria are common. The white blood cell count shows a rise due entirely to rise in lymphocytes, the percentage of which rises 25 or 30 per cent (MacKenzie and McEachern, 1938; Hatieganu *et al.*, 1939.)

Demonstration of excess of adrenaline in the blood. The first success was by Beer, King, and Prinzmetal (1937) perfusing the eviscerated rabbit's ear. Strombeck and Hedberg (1939) using a chemical method demonstrated a 30 times normal adrenaline content in the blood between attacks, with a 1000 times normal content in the attack. Earlier workers and also Biskind *et al.* (1941) were unable to find any pressor substance in the blood.

Duration and termination of paroxysms. The attacks may last minutes, hours, or days. The common length is one to two hours. The end of the attack may be marked by flushing of the face and neck, and abundant sweating, sometimes with salivation, lachrymation, and dilatation of the pupils. The blood pressure falls and after short attacks may reach a normal level in a few minutes.

After the paroxysm there is commonly a feeling of extreme prostration lasting from a few minutes up to several hours. Headache usually persists for some time after the attack.

Localized and minor paroxysms with symptoms of limited distribution are common; in these, however, closer investigation will often give evidence of symptoms or signs involving other systems.

Labbe, Tinel, and Doumer's patient attended for daily bouts of vomiting; Shipley's had diarrhoea and vomiting. Periodic nausea, headache, and abdominal pain immediately or an hour or two after meals, may be attributed to dyspepsia.

Angina pectoris is a common symptom and may be the most prominent. Palpitation may be the only complaint. Acute pulmonary oedema is not rare and in this disorder it may occur in the absence of cardiac enlargement or coronary artery disease. Shock or collapse may occur, as in the present case. In another case, during a paroxysm lasting three days, and giving a clinical picture of shock, the blood pressure varied between 90/70 and 240/150 without change in the general condition (van Goidsenhoven and Appelman, 1934). The cases resembling malignant hypertension are discussed below.

Severe headache, alone or with vomiting; and transient vertigo may occur by themselves. Transient loss of consciousness has been recorded in five cases, but all of these had persistently raised blood pressure. Periods of fatigue, lassitude, or weakness may be the salient feature (Fein and Carman, 1937; Hegglin and Nabholz, 1937). Sensations of anxiety may be the cause of consulting a physician (Palmer and Castleman, 1938).

Cases with lumbar pain and abnormal urinary findings; with recurrent glycosuria resistant to insulin; with bouts of malaise and pain; or with congestion of the face combined with profuse sweating; and other minor attacks are unlikely to be elucidated unless paroxysmal hypertension is found to accompany the symptoms, or a major crisis occurs.

Between attacks. Many subjects enjoy good health in the intervals. Loss of weight and anæmia (rarely severe) are common, and a persistently raised blood pressure is found in half the cases. Neutrophil leucocytosis, dyspepsia, or obstinate constipation may be seen. An abdominal tumour is present in one case in three. Fever occurs rarely. Lassitude or insomnia occur but anxiety is surprisingly rare.

The mode of death. The commoner modes of death after paroxysms are acute pulmonary oedema, shock or collapse, and cerebral hæmorrhage. Collapse may follow parturition or a minor operation under local anæsthetic (5 cases), or a major operation. Death with high fever is described. Chronic renal failure, Addison's disease, and malignant cachexia are rarer causes. Five cases have died suddenly and unexpectedly in hospital while undergoing investigation or awaiting operation.

Persistent hypertension. Some cases of pheochromocytoma from the start closely resemble malignant essential hypertension. Others have been followed from a stage in which hypertension occurred only in the attacks to a second stage of continuous hypertension with its usual sequelæ. The paroxysms may continue. If they do, symptoms are usually less widespread. Albuminuria, cylinduria, and azotæmia are common but may vary remarkably independently of the patient's symptoms. Even after it has been high for a long period, the blood pressure may fall to normal for a time (van Goidsenhoven and Appelman, 1934).

Electrocardiographic changes during attacks. Auricular premature beats (Rogers, 1933), runs of tachycardia of auricular and ventricular origin (Pincoffs, 1928), and sinus bradycardia with beats arising alternately from S-A and A-V nodes (Burgess *et al.*, 1936, Hegglin and Holzman, 1937) are recorded. A rapid arrhythmia during operation was seen by Hatieganu *et al.* (1939) and in the present case. QRS slurring (Allen, 1940) and left axis deviation (Kremer, 1936; Rogers, 1933) are recorded. The T wave varies; it may be very high (Pincoffs, 1928; Burgess *et al.*, 1936), flattened (Hegglin and Holzman, 1937), or inverted in leads I and II (Kremer, 1936; Allen, 1940; Rogers, 1933).

After attacks a remarkable lengthening of the S-T interval and variable changes in the T waves lasting a few days after severe attacks were noted by Hegglin and Holzman (1937). In the present case there was inversion of T in all leads lasting for some weeks after the attack. Neither inversion of T in all leads nor such slow recovery is described elsewhere.

Between attacks a normal curve was found in 6 of the 18 cases with reports. Very large P waves were noted in 3 cases, but left axis deviation and diminution or inversion of T were the most common findings. In the absence of repeated examinations it is not certain how permanent these changes were (cf. present case).

Where repeated curves have been taken (Rogers, 1933; Hegglin and Holzman, 1937) there have been notable variations in different attacks. The commonest change seen is flattening or inversion of the T wave in leads I and II. In two cases there was increased prominence of T waves. Experimentally adrenaline, usually but not always, gives increased T waves. The changes in rhythm seen in attacks are probably the resultant of A-V node acceleration from adrenaline and S-A node slowing due to the vagal effect from the depressor reflex. The T wave flattening seen in attacks is probably similarly a vagal effect. The S-T and T variations lasting for a few days after severe attacks observed by Hegglin and Holzman (1937) were considered to be due to metabolic upset in the myocardium. Similar temporary T wave depression may occur for a few days after a bout of paroxysmal tachycardia. The acute hypertension of acute nephritis may be associated with temporary changes in the T wave lasting some weeks. (Master, Jaffe, and Dack, 1936; Langendorf and Pick, 1938). These alterations, which are not exactly parallel to the rise in blood pressure, are probably partly due to the hypertension and partly toxic.

In the case reported here, Fig. 6A, taken a week after admission, showed dextrocardia, left axis

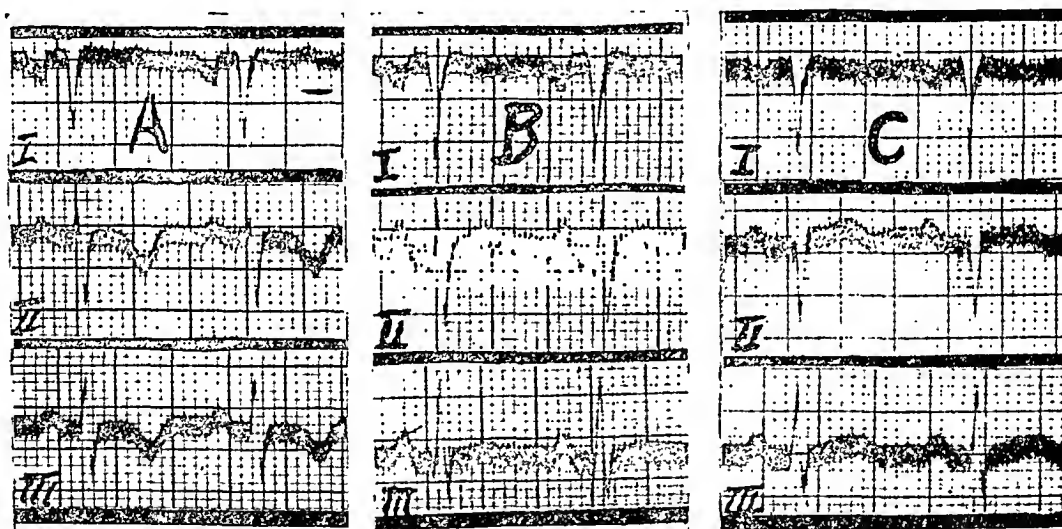


FIG. 6.—Case 1. Electrocardiograms: (A) 1 week after admission (8/7/41). (B) 8 weeks after admission (25/8/41). (C) Shortly before operation (20/9/41).

deviation, and inversion of T in all leads. These changes were still present three weeks later and were all thought to be associated with the dextrocardia (Schnitker, 1940), but eight weeks after admission the T waves were positive in all leads (Fig. 6B).

Depression of the T wave lasting some six weeks has not been previously described. It is unlikely to have been vagal or metabolic in origin; as it lasted too long. It may be analogous to that sometimes seen in acute nephritis, though T wave inversion in all three leads has not been reported in that disease. According to Goldzieher (1929), a large dose of adrenaline may produce myocardial lesions visible to the naked eye. Subepicardial hæmorrhages are recorded in autopsy findings after death in paroxysmal hypertension from pheochromocytoma. The long lasting T wave alterations seen in the present case were probably due to a small myocardial hæmorrhage, perhaps involving the conducting system.

DIFFERENTIAL DIAGNOSIS

The diagnosis rests on the history and the observation of an attack with paroxysmal hypertension and other phenomena. If spontaneous attacks are not seen, efforts should be made to induce one. Frequent readings of the blood pressure may detect symptomless paroxysms. The demonstration of excess adrenaline in the blood during or between crises is a specific test but is not always positive.

Intravenous injection of adrenaline may produce the same subjective feelings as an attack, but is not without danger. Estimation of serum potassium in the attack is suggested by McQuarry (quoted by Wells and Boman, 1937) since intravenous adrenaline may produce an 86 per cent rise in blood potassium figures. A very high value was found between attacks in the case recorded here. In deciding the site of the tumour, pyclography is much the most useful procedure. Perirenal pneumography is not recommended as it is hazardous and not very useful.

Paroxysmal hypertension occurs in a number of conditions. (1) *Pheochromocytoma*. (2) *Essential hypertension*. In this the blood pressure is always raised between the attacks, prodromes are common, the onset and end of the paroxysm are gradual, fits and cerebral eclipses are common, widespread symptoms are rare, and attacks are not precipitated by posture or pressure on the adrenals. Abnormal urinary findings and a leucocytosis are seen both in pheochromocytoma and in malignant hypertension. (3) *Symptomatic paroxysmal hypertension*. Recurrent attacks may occur in lead poisoning, eclampsia, tabes dorsalis, aortic reflux, angina pectoris, angina vasomotoria of Nothnagel, affections of the vagus, and thalamic tumour.

Where an attack has not been witnessed the history may be difficult to elucidate. Hyperthyroidism, diabetes mellitus, peptic ulcer, acute and chronic nephritis, malignant hypertension, surgical shock, polyarteritis nodosa, migraine, cerebral tumour, angina pectoris, cardiac neurosis, neurasthenia, and anxiety state may be simulated.

The vasovagal attacks described by Gowers (1907) and more recently by Ryle (1928) and Kinnier Wilson (1940) in some instances present a very close similarity to the attacks of the adrenal-sympathetic syndrome. Gowers considered that Nothnagel's syndrome was a closely allied phenomenon, and he pointed out that vasomotor spasm may attain a high degree in vasovagal attacks, being evidenced by coldness and pallor of the limbs and diminution of the pulse. Nothnagel's syndrome (see Lewis, 1931) is apparently identical in symptomatology with the adrenal-sympathetic syndrome. It is possible that some of Gowers' cases (e.g. his Case 1) and some of Nothnagel's were due to pheochromocytoma.

TREATMENT

The treatment of pheochromocytoma is to remove it. Laparotomy should be considered without undue delay as the benefits of successful removal of a pheochromocytoma outweigh the dangers of an operation in a case of secondary paroxysmal hypertension. Palliative treatment by sedatives or X-rays gives only transient relief.

Treatment of the paroxysm. Bleeding is most important. Morphine may be very valuable. Lumbar puncture will lower the blood pressure and relieve the headache in other types of paroxysmal hypertension, and should be useful in this one, especially for the headache which is severe and intractable. Vasodilators may give temporary relief, but worse discomfort later. For collapse following a paroxysm, adrenaline is specific (in contrast to its effect in surgical shock).

Pre- and post-operative measures. These are reviewed by Biskind *et al.* (1941). Chloroform, cyclopropane, and spinal anaesthesia should be avoided. The abdominal approach is recommended by most recent authors. Where the site of the tumour is uncertain, a laparotomy to locate the tumour and to establish the presence of the opposite adrenal body, with a later removal of the tumour by the lumbar route adds the real risk of a second operation but makes the actual excision a less disturbing procedure. This is important as operation may be accompanied by severe paroxysms. Incision of a large cyst may prevent these (Strombeck and Hedberg, 1939).

Operation was followed by severe shock in 17 of the 37 cases recorded. This shock is best combated by giving a dilute solution of adrenaline intravenously as described in the case report above. Where the blood pressure fails to respond to adrenaline, blood transfusion should be given. Salt and adrenal cortical hormone 10 c.c. should be given after operation.

Results of operation. In their excellent analysis of cases submitted to operation, Biskind, Meyer, and Beadner (1941) report 29 cases. The list is not quite complete: 3 cases (Belt and Powell, 1934; Volhard, 1931; Hatieganu *et al.*, 1939) which died after operation are excluded on inadequate grounds; 2 cases are omitted; one successful (Ody and Piotrowsky, 1933) and one fatal from post-operative shock (Keyser and Walters, 1924); and 3 successful operations have been recorded since (Brunschwig and Humphreys, 1940; Hamilton, 1940; and the present case).

If these cases are added, we get a total of 37 operations with 10 deaths. Of these 10 deaths after operation, 7 occurred in 19 cases reported to the end of 1936, and 3 in 18 cases reported since then.

Of the 27 survivors, 24 are probably quite well. In one case a recurrence of symptoms after operation responded to X-ray treatment (Borras and Meyer Mota, 1938).

DISCUSSION

The cause of the paroxysm or vascular crisis is a sudden hyperadrenalinæmia of obscure origin which causes a widespread vasoconstriction and also increases the output of the heart. The sharp rise of blood pressure acting through the "depressor" reflex leads to a vagal discharge, which explains why the symptom picture includes not only adrenergic mechanisms but also cholinergic ones such as salivation.

A rise of blood pressure without symptoms is probably common. Attacks with symptoms but no rise of blood pressure are mentioned by Labbé, Tinel, and Doumer (1922) and by Bernal (1933). These may occur but it is certain that in most of the paroxysms with only localized symptoms, it is the symptoms and not the vasoconstriction that are localized. This is shown by the rise in systemic blood pressure. The local symptoms are secondary to the rise of blood pressure; abdominal pain probably being due to distension of vessels, angina pectoris to oxygen deficiency in the overworking heart muscle, and so on.

Specific localization of symptoms is seen in other types of paroxysmal hypertension; abdominal in plumbism, cerebral in eclampsia, anginal in aortitis, but each of these is not invariable, e.g. eclamptics may complain of abdominal pain with their paroxysms.

A very striking symptom is the feeling of prostration, which may last for half an hour after an attack consisting of a few seconds' palpitation or dizziness. Freeman *et al.* (1941) and others have shown that on stopping adrenaline infusion in dogs, shock with oligæmia develops. Large doses of adrenaline may be followed by prolonged vagal effect (MacDowell, 1931). According to Goldzieher (1929, p. 81) pheochromocytoma may lead to complete exhaustion with morphological findings as in muscular overexhaustion.

Adrenaline in large doses diminishes muscle and somatic reflexes by a direct depressant action on the spinal cord (Schweitzer and Wright, quoted by Wright, 1942). This seems a likely explanation of the prostration, which is probably directly analogous to the "nervous exhaustion" felt after intense excitement.

The cause of the persistent hypertension sometimes seen with pheochromocytoma remains obscure. In continuous infusion of adrenaline, the blood pressure after an initial rise returns to normal (Freeman *et al.*, 1941). Strombeck and Hedberg (1939) in their case found the blood adrenaline between attacks was 30 times normal without persistent hypertension. But it is possible that in other cases there is a breakdown of the normal adrenaline destruction mechanism (see Richter, 1940) or there may be a dislocation of the normal mechanisms for regulating blood pressure. The common finding of albumen and casts in the urine after attacks suggests that renal damage sustained during paroxysms may be the cause, but this is doubtful. In some cases of pheochromocytoma with persistent high blood pressure, the kidneys at autopsy have been intact; in others after removal of the tumour the blood pressure has returned to normal, and in others it has returned to normal or below without operation.

On the other hand, it is possible that the vascular crises seen in essential hypertension, aortic valvular disease, tabes, eclampsia, and lead-poisoning, which may so closely resemble those of the adrenal-sympathetic syndrome, are themselves due to sudden discharge of adrenaline. Brandt and Katz (1933) reported that during hypertensive crises the blood has adrenergic characters on biological testing, which are absent between the crises. Bernal (1933) obtained a rise of blood pressure by perfusing blood taken from a patient with essential hypertension during a crisis, and also with blood taken from a patient during a bout of lead colic. These are experiments that should be repeated; especially as bleeding is the treatment for any hypertensive paroxysm.

SUMMARY

Two cases of adrenal-sympathetic syndrome due to pheochromocytoma (chromaffin tissue tumour of the adrenal medulla), are described.

The first is unusual in that though he had minor attacks almost daily for four years, there was only one major attack, which led to a diagnosis and operation, with cessation of the attacks.

The syndrome of chromaffin tissue tumours is reviewed. It is noted that while many cases show widespread symptoms, others show only local symptoms, though the vasoconstriction is generalized. Paroxysmal hypertension is the one sign common to all attacks. The treatment is removal of the tumour.

The close similarity between the hypertensive paroxysms of pheochromocytoma and those seen in other conditions, notably in essential hypertension, suggests that some at least of these other paroxysmal hypertension are due to sudden discharge of adrenaline.

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REFERENCES

Of 220 papers consulted, only those referred to in this paper are listed here. A fuller list and a table of published cases will be deposited in the library of the Royal Society of Medicine. A few more important references are starred.

- Allen, P. L. (1940). *Texas State J. Med.*, 36, 540.
 Beer, E., King, F. H., and Prinzmetal, M. (1937). *Ann. Surg.*, 106, 85.
 Belt, A. E., and Powell, T. O. (1934). *Surg. Gynec. Obstet.*, 59, 9.
 *Bernal, P. (1933). *Crises Hypertensives (thèse de Paris)*, G. Doin Paris, 1933.
 Bianchi, A. E. (1939). *Anales Inst. Modelo clin. Med.*, 20, 361.
 Binger, M. W., and Craig, W. McK. (1938). *Proc. Mayo Clinic*, 13, 17.
 *Biskind, G. R., Meyer, M. A., and Beadner, S. A. (1941). *J. Clin. Endocrinol.*, 1, 113.
 Borrás, P. E., and Mcyer Mota, M. (1938). *Sem. méd., B. Aires*, 1, 990.
 Brandt, F., and Katz, G. (1933). *Z. klin. Med.*, 123, 40.
 Brenner, F., Konzett, H., and Nagl, F. (1938). *Munch. med. Wschr.*, 85, 914.
 Brunschwig, A., and Humphreys, E. (1940). *J. Amer. med. Ass.*, 115, 355.
 Burgess, A. M., Waterman, G. W., and Cutts, F. B. (1936). *Arch. intern. Med.*, 58, 433.
 Burstein, C. L., Marangoni, B. A., De Graff, A. C., and Rovenstine, E. A. (1940). *Anesthesiology*, 1, 167.
 Bussell, L. J. (1940). *J. Pharm. exper. Therap.*, 69, 128.
 Christie, R. V. (1933). *Endocrinol.*, 17, 421.
 *Da Costa, A. C. (1939-40). *Ann. d'Endocrinol.*, 1, 337.
 *Edwards, D. G. ff. (1937). *J. Path. Bact.*, 45, 391.
 Ernould, H., and Picard, E. (1934). *Rev. belge Sci. méd.*, 6, 223.
 Fein, M. J., and Carman, F. F. (1937). *Amer. J. Cancer*, 29, 301.
 Foucar, F. H. (1939). *Amer. J. Path.*, 15, 741.
 *Frankel, F. (1886). *Virchows Arch.*, 103, 244.
 Freeman, N. E., Freedman, H., and Miller, C. C. (1941). *Amer. J. Physiol.*, 131, 545 (abstract in *Bull. War Medicine*, 1941, No. 6, p. 362).
 *Geschickter, C. F. (1935). *Amer. J. Cancer*, 23, 104.
 Goldzieher, M. A. (1929). *The Adrenals*, MacMillan & Co., New York.
 *Gowers, W. R. (1907). *The Borderland of Epilepsy*, J. and A. Churchill, London.
 Hamilton, J. E. (1940). *Kentucky med. J.*, 38, 572.
 Hatieganu, J., Moga, A., and Radu, P. (1939). *Bull. Acad. Méd. Roumanie*, 4, 179.
 *Hegglin, R., and Holzman, M. (1937). *Dtsch. Arch. klin. Med.*, 180, 681.
 Hegglin, R., and Nabholz, H. (1938). *Z. klin. Med.*, 134, 161.
 Hines, E. A. J., and Brown, G. E. (1933). *Ann. intern. Med.*, 7, 209.
 *Howard, J. E., and Barker, W. H. (1937). *Bull. Johns Hopk. Hosp.*, 61, 371.
 Jergensen, F. H. (1933). *Arch. Path.*, 16, 340.
 Kalk, H. (1934). *Klin. Wschr.*, 131, 613.
 Keyser, L. D., and Walters, W. (1924). *J. Amer. med. Ass.*, 82, 87.
 Kremer, D. N. (1936). *Arch. intern. Med.*, 57, 999.
 *Labbé, M., Tinel, J., and Doumer (1932), *Bull. Soc. méd. Hôp. Paris*, 46,, 982.
 Langendorf, R. and Pick, A. (1938). *Acta med. Scand.*, 94, 1.
 Lazarus, J. A., and Eisenberg, A. A. (1932). *J. Urol.*, 27, 1.
 *Lewis, T. (1931). *Heart*, 15, 305.
 McDowell, R. J. S. (1931). *J. Physiol.*, 71, 417.
 MacKenzie, D. W., and McEachern, D. (1938). *J. Urol.*, 40, 467.
 Master, A. M., Jaffe H. L., and Dack, S. (1936). *Amer. Heart J.*, 12, 244.
 Nuzum, F. R., and Dalton, J. W. (1938). *Ibid.*, 16, 643.
 Ody and Piotrowski (1933). *Bull. Soc. nat. Chirur.*, 59, 1220.
 *Palmer, R. S., and Castleman, B. (1938). *New Engl. J. Med.*, 219, 793.
 *Peyron, A. (1930). *Bull. Assoc. franç. Cancer*, 19, 618.
 Pincoffs, M. C. (1929). *Trans. Assoc. Amer. Phys.*, 44, 295.
 Plazy and Germain (1932). *Bull. Soc. méd. Hôp. Paris*, 48, 891.
 Richter, D. (1940). *Proc. Roy. Soc. Med.*, 33, 615.
 Rimbaud, P., and Delmas, A. (1939). *Bull. Assoc. franç. Cancer*, 28, 682.
 Rogers, E. (1933). *Amer. Heart J.*, 8, 269.
 Rowntree, L. G., and Ball, R. G. (1933). *Endocrinol.*, 17, 263.
 Ryle, J. A. (1928). *Guy's Hosp. Reports*, 78, 371.

- Schnitker, M. A. (1940). *The Electrocardiogram in Congenital Heart Disease*, Harvard Univ. Press, Cambridge, Mass, p. 23.
- Strombeck, J. P., and Hedberg, T. P. (1939), *Acta Chir. Scand.*, **82**, 177.
- *Van Goidsenhoven, F., and Appelman, R. (1934). *Bull. Acad. Méd. Belg. 5e serie*, **14**, 672.
- Vaquez, H., Donzelot, E., and Géraudel, E. (1929). *Presse méd.*, **37**, 169.
- Volhard, F. (1931). *Handb. d. inn. Med. von v. Bergmann u. Staehelin T. I* 338 ; *T. II* 1742, Julius Springer, Berlin.
- Walters, W., and Kepler, A. D. (1938). *J. Amer. med. Ass.*, **111**, 1061.
- Weber, F. Parkes (1920). *Practitioner*, **105**, 181.
- Wells, A. H., and Boman, P. G. (1937). *Ibid.*, **109**, 1176.
- Weyrauch, H. M., Jr. (1940). *Ibid.*, **114**, 652.
- Wiesel, J. (1909). *Mitt. d. Gesellsch. phys. Med., Wien*, **2**, 24.
- Wilson, S. A. K. (1940). *Neurology*, Vol. II, p. 1505, Arnold, London.
- Wright, S. (1940). *Applied Physiology*, Seventh edition, Oxford Medical Publications, p. 195.

RECIPROCAL BEATING INITIATED BY VENTRICULAR PREMATURE SYSTOLES

BY

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Reciprocal rhythm is a rare phenomenon. All reported cases with but one exception are instances of nodal rhythm with re-entry of the retrograde nodal impulse (1-3, 5-10, 12, 15, & 21-24). However, Wolferth and McMillan (1939) have described a case of sinus rhythm with re-entry of the antegrade sinus impulse. In the present communication a unique case is reported in which the reciprocal rhythm was initiated by ventricular premature systoles. So far as we are aware, this has not been described before in a human heart although it has been produced in the experimental animal (14, 17, & 19). The patient manifesting this arrhythmia was a 56 year old white woman (a private patient of Dr. D. C. Straus) who presented no evidence of organic heart disease and was sent up for analysis of her pulse irregularity. In Fig. 1 is shown her first cardiogram and in Fig. 2 records taken during and after left carotid sinus pressure and after exercise.

Fig. 1 shows a group of four ventricular beats which repeat themselves throughout, except at the end of lead III. The four QRS complexes in each group will be called R_d , R_e , R_f , and R_g respectively, and the three P waves, P_a , P_b , and P_c respectively.

It will be seen that P_a and P_b precede R_d and R_e and that the P_a - R_d and P_b - R_e intervals are constant in each lead and measure 0.14 sec. in lead II (0.08 sec. when measured from the peak of P to QRS onset). Further, the P_a - P_b intervals vary slightly; in lead I from 0.92-0.94 sec., in lead II from 0.90-0.94 sec., in lead III from 0.86-0.90 sec., and in the chest leads from 0.90-0.92 sec. The mechanism for the first two beats of the groups of four is therefore a sinus arrhythmia varying in rate from 64 to 70 beats per minute.

The third ventricular beat, R_f , is obviously a premature ventricular systole since it is premature, is not preceded by a P wave, and is prolonged and bizarre compared to R_d and R_e .

The fourth ventricular beat, R_g , is preceded by a P wave, P_c , in every instance, and it resembles R_d and R_e closely. Three types of P_c are seen:

- (a) one that resembles P_a and P_b making allowances for the fact that P_c occurs superimposed on the S-T-T complex of R_f , viz. the second P_c in (C), the third P_c in (D), and probably all the P_c waves in (A);
- (b) one that is strikingly different from P_a and P_b . This is best seen in leads II and III where it is sharply inverted while P_a and P_b are upright, viz. the second P_c in (B) and the first P_c in (D);

and (c) one that is intermediate in contour between (a) and (b), viz. the first and third P_c in (B), the first and third P_c in (C), and the second and fourth P_c in (D).

All three types of P_c are characterized by a tendency towards prematurity, viz. P_b - P_c is shorter than P_a - P_b . The P_c - R_g interval and the R_f - P_c intervals are not easily measured because the beginning of P_c cannot be located exactly. However, by comparing the intervals

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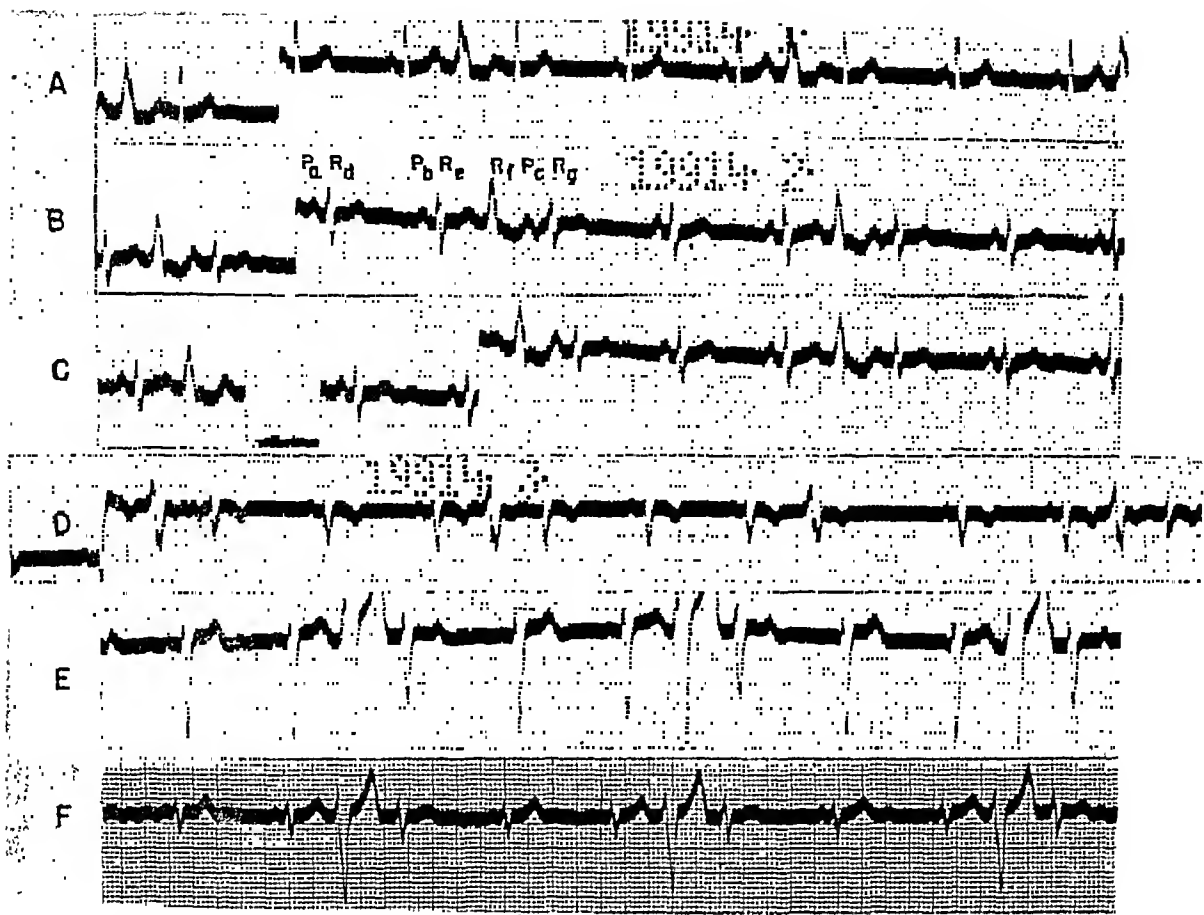


FIG. 1.—Electrocardiogram from the patient at his first visit. (A) is lead I; (B) and (C) are a continuous strip of lead II, the last beat of (B) being repeated as the first beat of (C). In (B) a group $P_a, R_a, P_b, R_b, R_f, P_c, R_g$ is labelled. Discussed in text. (D), (E), and (F) are respectively leads III, CF_2 , and CF_4 . Note that P_c in the chest leads (E and F) is difficult to make out.

measured from the peak of P_c with similar measurements made from the peak of P_a and P_b , it is apparent that P_c-R_g (0.08–0.16 sec.) is equal to or longer than P_a-P_d and P_b-R_e . The R_f-R_g interval is constant for each lead, regardless of the position and contour of the intervening P_c . In leads I and the chest leads it equals 0.50 sec. and in leads II and III, 0.52 sec. Likewise such measurements show that R_f-P_c is equal to about 0.28–0.44 sec.; in those instances where P_c is inverted R_f-P_c is constant and measures 0.44 sec., and the same value is obtained in the third P_c in lead II where P_c is intermediate in contour between P_a and the inverted P_c ; in all other instances R_f-P_c is shorter than 0.44 sec. and the contour of P_c varies.

On one occasion in lead III, P_c is not followed by R_g . In this latter instance P_c resembles P_a and P_b , and R_f-P_c is equal to 0.28 sec. R_f occurred later than usual in this instance, viz. R_e-R_f here equals 0.52 sec. as compared with the usual value of 0.41–0.44 sec. in the limb leads and 0.48 sec. in the chest leads.

At first sight the beat P_cR_g might be considered an auricular premature systole when P_c is abnormal, and a sinus beat when P_c resembles P_a and P_b . In the former case, we would be dealing with a pair of premature systoles, the first, R_f , a ventricular, and the second, P_cR_g , an auricular. In the latter case, we would be dealing with an interpolated ventricular premature systole, R_f . However, closer examination of the record and its measurements, together with the data obtained in the later records (see below) are opposed to this interpretation. The argument for the alternative interpretation we adopted is along the following lines.

The bizarre P_c waves resemble in contour retrograde P waves which are usually small and upright in lead I and sharply inverted in leads II and III. They are therefore considered

retrograde P waves. Such retrograde P waves could be due either (a) to retrograde conduction of the impulse from the ventricular premature systole R_f or (b) to retrograde conduction of an impulse arising in the A-V node which gives rise to R_g . Since a nodal premature systole, as assumed in (b) which shows fixed coupling with the preceding QRS, is most likely due to re-entry, the alternative explanations for the retrograde P waves become identical.

The acceptance of the view that the bizarre P waves are retrograde in origin permits consideration of the P_c intermediate between the bizarre ones and those resembling the sinus P waves. The intermediate P_c waves can be considered to be due to simultaneous invasion of the auricles from the sinus node and by the retrograde impulse. A comparable phenomenon seen in the transition from sinus to A-V nodal rhythm has led to the description of such beats as transitional complexes (Lewis, 1925), or fusion beats (Katz, 1941). The alternative explanation for the variable P_c contour would be to ignore the retrograde contour and conceive the P_c complexes as being auricular premature systoles from varying foci. The latter explanation is not as tenable as the fusion P assumption since it ignores the constancy of R_f-R_g regardless of the P_c contour and would not explain the occurrence of a P_c-R_g interval of less than 0.12 sec. in a subsequent record (Fig. 2 A).

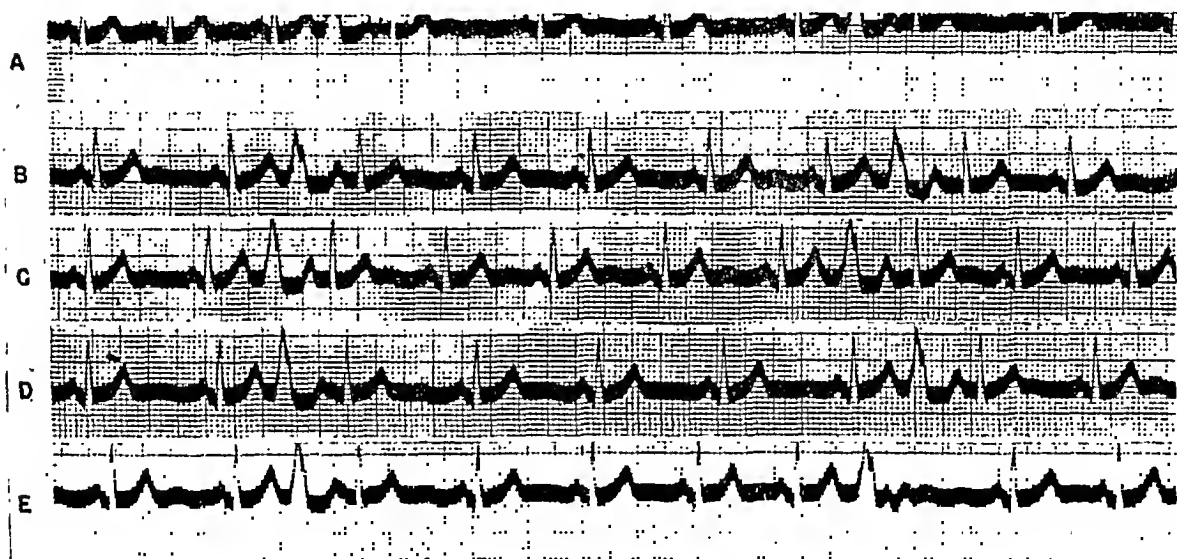


FIG. 2.—Electrocardiograms (lead II) taken one month after that shown in Fig. 1. (A) is a record at rest and shows two instances where P_c-R_g is less than 0.12 sec. (B) is a record after exercise, and (C) during left carotid sinus pressure. They show that R_f-R_g (second pair in each strip) is longer than the R_f-R_g interval obtained in records at this time. (D) is also taken during left carotid sinus pressure. R_f-R_g in this strip, as in the first pair of (B) and (C) and both pairs in (A) show the usual duration found at this time. (E) taken immediately after left carotid sinus pressure shows one R_f-P_c combination not followed by R_g . The P_c in this instance is clearly of sinus origin. Discussed in text.

If the view that P_c waves differing from P_a and P_b in contour are associated with retrograde conduction, then the R_g that follows such a P_c cannot be of sinus node origin, since the sinus node impulse either does not invade the auricles or at least does not reach the A-V junctional tissues. R_g must therefore be due to the retrograde impulse responsible for P_c and hence is part of a reciprocal rhythm initiated by the premature ventricular systole R_f .

There remains the group of P_c waves which are almost identical with P_a and P_b . Two alternatives exist for R_g following such P waves. In fact both might be operative on different occasions. The simpler explanation would be to assume that R_g is of sinus node origin. In favour of this view is the fact that in subsequent records there were three occasions on which R_f-R_g , otherwise remarkably constant, was prolonged compared to the other R_f-R_g intervals and associated with a P_c-P_g longer than the usual sinus P-R, as might be expected after an interpolated ventricular premature systole (e.g. the second group in Fig. 2 B and Fig. 2 C). In

these three instances R_g is most likely of sinus origin. The remarkable constancy, with the three exceptions noted, of the R_f - R_g interval (regardless of the position and contour of P_c) favours the idea that R_g is part of a reciprocal rhythm. This reciprocal rhythm is initiated by R_f and re-entry to the ventricles of the retrograde impulse occurs at a point below the auricles somewhere in the A-V junctional tissues above the bifurcation of the common A-V bundle at a time before the sinus impulse reaches the re-entry point.

Several other facts became apparent in the series of records (of lead II only) taken a month after Fig. 1 which support our explanation. These were recorded during rest, after exercise, during and after left carotid sinus pressure, and during the first 45 minutes of the action of atropine sulphate (1/75 grain intramuscularly) (Fig. 2).

(1) In these records a total of 91 R_f complexes were encountered, the P_c that followed was of sinus contour in 87, retrograde in none, and suggested a fusion P in 4. In 38 instances a combination $R_fP_cR_g$ occurred.

(2) There was a sinus arrhythmia present with slight variations of P contour indicating a wandering pacemaker, but the P_c contour (even allowing for the distortion due to its superposition on the S-T-T of R_f) varied more than the sinus P waves.

(3) There was a shortening of the P - P_c interval and a lengthening of the P_c - P interval apparently due to the same mechanism as so-called ventriculo-phasic sinus arrhythmia in heart block.

(4) The occurrence of R_g depended on the R_f - P_c interval. R_f - P_c varied from less than 0.16 to 0.32 sec. when R_g was absent, and from 0.34 to 0.42 sec. when R_g followed. The variations in R_f - P_c were due to the sinus arrhythmia as well as to the occurrence of the premature ventricular systole, R_f , at different times after the sinus QRS, i.e. R_c - R_f varied from 0.36-0.56 sec.

(5) In all instances where P_c was not followed by R_g , P_b appeared to be of sinus origin.

(6) The interval R_f - R_g was remarkably constant, being 0.48 sec. In three instances it was longer, equalling 0.51, 0.52, 0.52 sec. (Fig. 2 B & C). In these three, P_c occurred relatively early (at the shortest R_f - P_c distance followed by an R_g), resembled the sinus P, and was associated with a prolonged P_c - R_g interval (0.15, 0.18, 0.18 sec. respectively) as compared with other P_c - R_g intervals (0.06-0.14 sec.). These facts confirmed the view that R_fR_g represent reciprocal rhythm except when the R_f - R_g interval is definitely prolonged; in the latter case, R_g is considered to be of sinus origin. This has already been referred to above.

(7) The occurrence of P_c - R_g of less than 0.12 sec. was encountered three times (Fig. 2 A), indicating that R_g in these instances can not be of sinus origin, nor due to any impulse spreading from the auricles to the ventricles after the inscription of P_c , a matter already referred to above. In determining the position of P in this and other instances, a task not always easy, we made use of the duration of electrical systole of R_f in other beats in the record.

The mechanism which we believe underlies this arrhythmia can best be summarized diagrammatically as in Fig. 3. A sinus rhythm is present throughout and in addition there are ventricular premature systoles; these two pacemakers determine the arrhythmia. The ventricular premature beats have retrograde conduction and the contour of P_c following them will depend upon where the retrograde impulse and sinus impulse meet and interfere with each other. This is determined by the relative time of discharge of the sinus and ventricular pacemakers and by the retrograde conduction time. The possibilities are:

(a) near the sinus node (Fig. 3 A) in which case the auricles will be controlled by the retrograde impulse and P will have the retrograde P contour;

(b) near or within the A-V junctional tissue (Fig. 3, C, D, and E) in which case the auricles will be controlled by the sinus impulse and P will be of sinus P contour; or

(c) somewhere in the auricles (Fig. 3 B) in which case the auricles will be controlled in part by the sinus and in part by the retrograde impulse and P will have a contour intermediate between the sinus and retrograde P, i.e. it will be a fusion P.

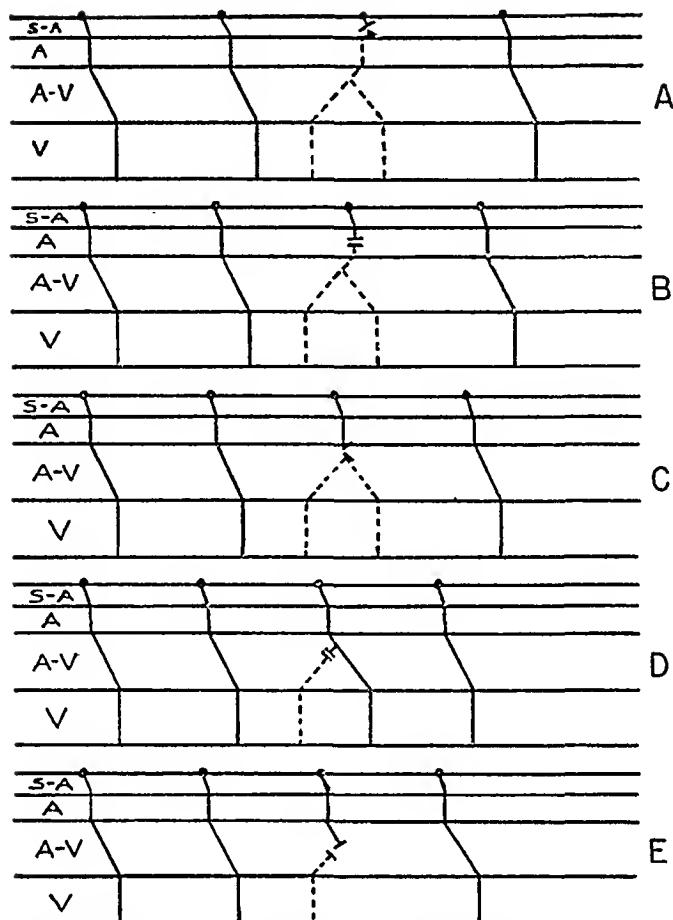


FIG. 3.—A series of diagrams illustrating the various circumstances encountered in this patient, showing the various locations of interference between the sinus and retrograde impulses as well as the conditions under which re-entry and reciprocal rhythm are established. Discussed in text. Dotted lines represent the ventricular premature systole, the retrograde conduction, and the re-entry leading to reciprocal rhythm. S-A, A, A-V, and V represent conduction respectively within the sinus node, auricles, A-V junction, and ventricles.

The retrograde impulse in travelling through the A-V junctional tissue finds a point at which it can become antegrade again and re-enter the ventricles. The fact, pointed out above, that the interval R_f-R_g is fixed except on three occasions begs coincidence too much and suggests that in all but the three exceptions the combination of the premature ventricular systole and the ventricular beat that follows are instances of reciprocal rhythm. Since this occurs at times when the auricles are under the control of the sinus node and not invaded by the retrograde impulse from the premature ventricular systole, and at other times when P_c suggests a fusion P, with a P_c-R_g interval of less than 0.12 sec., it follows that re-entry takes place below the auricles in these cases, and therefore presumably this is the location of re-entry in all cases where reciprocal rhythm occurs. Further the fact that the second ventricular complex of the reciprocal rhythm resembles those of sinus origin indicates that the re-entry point is above the bifurcation of the common bundle. It is our inclination to believe that it is somewhere in the A-V node where branching is more prevalent than in the A-V bundle. The conditions for re-entry have been clearly analysed by Schmitt and Erlanger (1928) as a monodromic condition in some fibers with a heterodromic condition in adjacent fibers. In other words different degrees of unidirectional block in adjacent fibres predispose to re-entry of the impulse. In our case the retrograde conduction time (R-P) of about 0.40 sec. in those instances where P_c is retrograde (Fig. 1), as compared to a P-R of 0.14 sec. of the sinus beats proves that retrograde conduction is markedly delayed.

We are now prepared to consider what happens in the A-V junctional tissue in those beats

in which the sinus impulse invades it after the premature ventricular systole is initiated. Two main possibilities exist.

The sinus impulse can meet the retrograde impulse before the latter has passed the point of re-entry, and so prevent not only the retrograde impulse from entering the auricles but also the establishment of the reciprocal rhythm. If the sinus impulse enters sufficiently early it itself will be prevented from entering the ventricles and the ordinary variety of premature ventricular systole with a fully compensatory pause will ensue (Fig. 3 E). If, however, the sinus impulse enters later so as to reach the point of re-entry just ahead of the retrograde impulse, it may find the tissue through which the retrograde impulse usually re-enters in a state permitting its passage into the ventricles. Here, then, the re-entry would be prevented but a second ventricular complex would follow the premature ventricular systole at an interval somewhat longer than that between the ventricular beats of reciprocal rhythm, because of prolongation of the conduction through the A-V junction resulting from the fact that the sinus impulse travels through earlier than the re-entry impulse (Fig. 3 D). This then would be an example of an ordinary interpolated ventricular premature systole.

The sinus impulse can meet the retrograde impulse after the latter has passed the point of re-entry. In this case, the sinus impulse would prevent the retrograde impulse entering the auricles, and the retrograde impulse would prevent the sinus impulse from reaching the ventricles. However, since re-entry had occurred, the retrograde impulse would actually cause the following ventricular beat. In short, the post-extrasystolic beat would have a sinus P wave and a ventricular complex due to re-entry of the retrograde impulse of the preceding premature ventricular systole, the P and QRS thus being unrelated (Fig. 3 C). In these cases the R-R interval between the two beats of the reciprocal rhythm would be expected to have the same duration as in those cases in which a retrograde P can be shown to occur between them; and this was actually true.

The occurrence of re-entry before the impulse reaches the auricles, found in our case, may be found in any case of reciprocal rhythm, as Drury (1924) suggested and as has been postulated by Scherf and Shookhoff (1926) and by Cutts (1937). The case of Gravier *et al.* (1939) showing reciprocal rhythm and varying P wave contour could be explained, in like manner, by assuming re-entry below the auricles with interference between the retrograde and sinus impulses above the level of re-entry. Obviously, the "sandwiching" of the P wave between two ventricular complexes (White, 1915) does not constitute an integral part of reciprocal rhythm. Even when such a P wave is retrograde in character it indicates merely retrograde conduction, a condition necessary for re-entry.

The significance of a sinus P between a pair of ventricular beats in a case like ours may be evaluated by the duration of the P-R interval compared with the P-R of the sinus beats. When the P-R is equal to or shorter than the sinus P-R, the second beat would be considered a reciprocal beat, provided the R-R interval equalled that of known reciprocal beats. When the P-R is longer than the sinus P-R duration and the R-R interval is also prolonged while P resembles the sinus P waves, then, the second beat would be considered a sinus beat. The fortuitous combination of a sinus P wave between two ventricular beats indicates "pseudo-reciprocal rhythm" (Katz and Kaplan, 1938).

The case reported by us suggests that even in the absence of retrograde conduction in the form of retrograde P waves, re-entry may be responsible for other instances of fixed coupling, whether this occurs as in our case between two premature systoles or between a premature systole and the preceding sinus beat. This possibility though previously considered (Mines, 1913; de Boer, 1921; and Lewis, 1925) has been questioned by others (Scherf, 1930, and Rothberger, 1931). Our case is important since it definitely favours the re-entry mechanism. When the second ventricular complex is bizarre compared with the sinus beats the re-entry may be below the bifurcation of the common bundle, and this variety is the common one encountered. Probably other instances like ours will be discovered.

SUMMARY AND CONCLUSIONS

A case is presented showing sinus rhythm and ventricular premature systoles followed at a fixed interval by another premature ventricular complex of supraventricular origin. The occasional presence of inverted P waves between the two premature ventricular beats suggested reciprocal rhythm. This was substantiated not only by the constant interval between the two premature ventricular beats but also by the occurrence of P waves preceding the second premature ventricular beat at a distance so short as to preclude the possibility of conduction of an impulse from the auricles to the ventricles in the second beat.

In our case evidence is presented to suggest that the point of re-entry was below the auricles and above the bifurcation of the common bundle, presumably within the A-V node.

It is pointed out that the retrograde P waves in cases of reciprocal rhythm due to re-entry of retrograde impulses merely indicate the presence of retrograde conduction, without in themselves constituting an essential part of the mechanism underlying reciprocal rhythm.

The various possibilities of interference, in our case, between the sinus impulse and retrograde impulses causing reciprocal rhythm are evaluated and instances of each cited.

Our case indicates that instances of fixed coupling of premature ventricular beats even in the absence of P waves, indicative of retrograde conduction, may be examples of re-entry.

REFERENCES.

1. Bishop, L. F. (1921). *J. Amer. med. Ass.*, **77**, 31.
2. Blumgart, H. L., and Gargill, S. L. (1930). *Amer. Heart J.*, **5**, 424.
3. Cutts, F. B. (1937). *Ibid.*, **14**, 717.
4. De Boer, S. (1921). *Arch. ges. Physiol.*, **187**, 193.
5. Dock, W. (1928). *Arch. intern. Med.*, **41**, 745.
6. Drury, A. N. (1924). *Heart*, **11**, 405.
7. Fogelson, L. J. (1929). *Z. Kreislaufforsch.*, **21**, 290.
8. Gallavardin, L., and Gravier, L. (1921). *Arch. Mal. Coeur.*, **14**, 71.
9. Gravier, L., Froment, R., and Guiran, J. B. (1939). *Ibid.*, **32**, 622.
10. Katz, L. N., and Kaplan, L. G. (1938). *Amer. Heart J.*, **16**, 694.
11. Katz, L. N. (1941). *Electrocardiography*, Philadelphia.
12. Korth, C., and Schrumphf, W. (1936). *Dtsch. Arch. klin. Med.*, **178**, 589.
13. Lewis, T. (1925). *The Mechanism and Graphic Registration of the Heart Beat*, 3rd ed. London.
14. Mines, G. R. (1913). *J. Physiol.*, **46**, 349.
15. Reid, W. D. (1930). *Amer. Heart J.*, **5**, 524.
16. Rothberger, C. J. (1931). *Ergeb. Physiol.*, **32**, 681.
17. Scherf, D., and Shookhoff, Ch. (1926). *Wien. Arch. inn. Med.*, **12**, 501.
18. Scherf, D. (1930). *Z. ges. exper. Med.*, **70**, 375.
19. — (1941). *Arch. intern. Med.*, **67**, 372.
20. Schmitt, F. O., and Erlanger, J. (1928). *Amer. J. Physiol.*, **87**, 326.
21. Samojloff, A., and Tschernoff, A. (1930). *Z. ges. exper. Med.*, **71**, 768.
22. v. Dobozs, E. (1936). *Klin. Wschr.*, **15**, 1160.
23. White, P. D. (1915). *Arch. intern. Med.*, **16**, 517.
24. — (1921). *Ibid.*, **28**, 213.
25. Wolferth, C. C., and McMillan, T. M. (1939). *Amer. Heart J.*, **4**, 521.

HEART FAILURE IN THE AGED

BY

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Heart failure in old age differs in many ways from that in earlier life. Aetiology, pathology, course, symptoms, and treatment are all modified by the special circumstances. For example, rheumatic disease and syphilitic disease are not common over the age of sixty; but toxæmia, especially after pneumonia, becomes an important factor. Before middle age, the pathological state of the heart itself is all important: after this, the condition of the peripheral vessels also must be taken into account. In the young, recovery is more rapid and lasting: in the old, relapses are the rule and not the exception. Congestive failure with "back pressure" is the chief form of failure in early life: but ischæmic failure, as angina pectoris and coronary thrombosis, becomes more frequent as old age approaches. The present paper is an analysis of the history of cardiac failure in seventy-five old or elderly persons, and attempts to point out the special characteristics arising in senility. Owing to lack of post-mortem facilities in war time, only the clinical features are available for consideration.

AETIOLOGY

The series was composed of 75 patients whose ages ranged from sixty-two to ninety-two. All were males and all but five were Chelsea pensioners. No congenital or rheumatic heart disease was found, and the youngest patient was the only one with syphilitic heart disease. The commonest cause of cardiac failure was a high blood pressure, which was the sole factor, apart from arteriosclerosis, in 27 cases. Coronary arterial disease alone accounted for 13, while coronary disease and hypertension were found together in 4 cases. A toxic myocardium, resulting from pneumonia or some other infection, was the cause of failure in 11 cases, 2 of them having had hypertension previously and 2 others having had previous coronary thrombosis. The remainder were originally classed as "myocardial degeneration," but more careful study of their records enabled them to be analyzed more precisely. Six of these were probably due to past high blood pressure. Each had the heart enlarged to the left, and was admitted to hospital with a blood pressure that continued to fall until death. Two more followed long standing asthma and chronic bronchitis, so were classified as chronic cor pulmonale. One was a heart block of unknown cause. One showed increasing peripheral ischæmia with a blood pressure that fell steadily until death. All the rest showed congestive heart failure, complained of dyspnœa on exertion, had no raised blood pressure, and never had pain in the chest or arm on effort; this, or course, may have been because they never exerted themselves enough. These results are summarized in Table I.

TABLE I

AETIOLOGY OF HEART FAILURE IN THE OLD

| | |
|---|----------|
| Hypertension alone (including 6 where the diagnosis was "probable past hypertension") .. | 33 |
| Coronary disease (alone 13, and with hypertension 4) | 17 |
| Myocardial toxæmia | 11 |
| Various (chronic cor pulmonale 2, heart block (? cause) 1, syphilitic heart disease 1, and uncertain, 10) | 14 |
| | <hr/> 75 |

VARIETIES OF FAILURE

While congestive failure, anginal failure, and coronary thrombosis are among the commoner forms of cardiac defeat, other varieties peculiar to senility also occur. These seem to result from the inability of the left ventricle to propel the blood against the increased resistance of the thickened and narrowed peripheral arteries. The basic pathology shows itself as peripheral ischæmia, sometimes intermittent, sometimes constant, and sometimes progressive. Steiglitz (1935), in his book *Abnormal Arterial Tension*, refers to this conception as relative hypotension. The dominant symptoms are usually cerebral in origin. One symptom-complex of this type has already been described by the present writer (1941 and 1943) under the name of progressive cerebral ischæmia. Here, an arteriosclerotic patient with high blood pressure shows first mental confusion, then restlessness or violence, and finally becomes comatose while his systolic figure falls from its previous high grade to the ultimate level (around 100 mm.) at which death ensues in such cases. This syndrome may follow right or left heart failure which has been treated with apparent success, or may result from myocardial toxæmia after an infection, such as pneumonia. This latter occurrence was mentioned by a former physician to the Royal Hospital in 1863.

One other form of "forward" failure requires notice. This is the gradual but steadily increasing feebleness, accompanied by a slowly falling blood pressure, seen in a few patients. There is no angina pectoris, no congestive failure, no paroxysmal dyspnœa, nor are cerebral symptoms prominent. As the great Harvey says in Chapter 3 of *De Motu Cordis et Sanguinis*—"When this (left) ventricle contracts languidly, the pulse in the arteries is scarcely perceptible."

The varieties of heart failure are summarized in Table II.

TABLE II

| VARIETIES OF FAILURE IN THE OLD | | | | | |
|---|----|----|----|----|----------|
| Left heart failure (paroxysmal dyspnœa) | .. | .. | .. | .. | 16 |
| Right heart failure (congestive) | .. | .. | .. | .. | 13 |
| Right and left heart failure together | .. | .. | .. | .. | 9 |
| Coronary thrombosis | .. | .. | .. | .. | 10 |
| Angina pectoris | .. | .. | .. | .. | 4 |
| Coronary ischæmia and right heart failure | .. | .. | .. | .. | 3 |
| Cardiac stoppage | .. | .. | .. | .. | 3 |
| Progressive cerebral ischæmia alone | .. | .. | .. | .. | 12 |
| Other forward failure | .. | .. | .. | .. | 5 |
| | | | | | <hr/> 75 |

Other cases, provisionally labelled as relative hypotension, have been excluded from the present series. This was on account of the difficulty in separating them clearly from what might be termed arteriosclerotic dementia. Such patients often die a non-cardiac death, e.g. from hypostatic pneumonia or enteritis. In practice, hypostatic pneumonia must be distinguished from pulmonary œdema of cardiac origin. The latter benefits from the administration of mersalyl as a rule: the former often seems to be made worse by it.

DISCUSSION

The first point which appears from the consideration of the above facts and figures is the frequency of multiple ætiology, when compared with causes of heart failure in young persons. Arterial thickening probably played a part in most of the cases, usually in association with hypertension or disease of the coronary artery. Sometimes myocardial toxæmia was super-added on top of these causes, and this made a fatal prognosis almost inevitable. Secondly, no less than 13 per cent of the cases had heart failure of which the cause was uncertain, even after repeated clinical examination. Although the term "myocardial degeneration" is deservedly disliked by cardiologists, some label must be applied to those cases of congestive failure whose cause cannot be determined during life with any degree of certainty. Arterio

sclerosis can be considered as playing a part both as external resistance to the output of the left ventricle and also by lessening the nutrition of the myocardium. Yet cases are often met, with thickened and tortuous arteries, who do not complain of any discomfort in chest or arm on normal exertion. This absence of symptoms of angina pectoris has been remarked by previous medical officers at the Royal Hospital (Lipscombe, 1932). Out of the four patients in the series, one was a private case and one followed coronary thrombosis; while the time taken to collect the total of seventy-five was over four years.

As noted above, high blood pressure is the commonest cause of heart failure in the series. This is as one would expect, since between forty and fifty per cent of Chelsea pensioners show a systolic pressure above 160 mm. Such cases die in congestive failure (52 per cent), from myocardial toxæmia (11 per cent), with progressive cerebral ischæmia (33 per cent), or with a gradually falling blood pressure (4 per cent). In the patients with congestive failure, the right ventricle was affected as often as the left, which suggested that the hypertension was not the only factor to be considered.

The final impression remaining was that the level of the blood pressure and the state of the arteries were the two deciding factors in prognosis. Once the former was unable to overcome the resistance of the latter, ischæmia of vital organs was present. Clinically, this usually showed itself by increased restlessness and a desire to get in and out of bed repeatedly without reason. When this occurred, a fatal termination was not far off.

SUMMARY

The causes and forms of heart failure in 75 old persons are described.

The commonest causes of failure were high blood pressure, disease of the coronary artery, and myocardial toxæmia.

In 13 per cent of the cases, the cause of heart failure remained uncertain after repeated clinical examination.

The occurrence of "forward" heart failure, with peripheral ischæmia is described; and the importance of arteriosclerosis in producing circulatory failure is stressed.

REFERENCES

- Harvey, W. (1628). *De Motu Cordis et Sanguinis*.
 Howell, T. H. (1941). *Postgrad. med. J.*, 17, 195.
 Howell, T. H. (1943). *Brit. med. J.* (in press).
 Lipscombe, F. M. (1932). *Diseases of Old Age*, London.
 Maclachlan, D. (1863). *A Practical Treatise on the Diseases and Infirmities of Advanced Life*, London.
 Steiglitz, E. J. (1935). *Abnormal Arterial Tension*, New York.

A CASE OF MYXOMA OF THE LEFT AURICLE

BY

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In their paper on this subject Fawcett and Ward (1939) remark that only rarely do descriptions of this interesting lesion appear in British publications, there being only one report in the nine years preceding their article. The condition is well reviewed in their paper and in that of Gilchrist and Millar (1936). It is the purpose of this article to describe a further case with an autopsy report.

DESCRIPTION OF THE CASE

The patient, a woman of 33 years of age, was admitted to hospital with severe cardiac failure. There was a story of "growing pains" at the age of 17, but no history of rheumatic fever or of chorea. The family history was of no significance.

Her earliest complaint, which was of shortness of breath on exertion, started a year before admission; there was also a two-months' story of palpitation and swelling of the feet in the evenings. She managed to continue her work about the house until five weeks before admission, when on her doctor's advice she retired to bed. All these symptoms continued with the addition of a productive cough, loss of appetite, thirst, a feeling of "fullness and wind" in the abdomen, and great discomfort when lying flat in bed, this necessitating her being propped up on pillows.

On examination she was dyspnoeic and cyanosed with an obvious malar flush. The neck veins were greatly distended but were not pulsating. There was no clubbing of the fingers. There was a mild degree of oedema of the legs, sacrum, and back, up to the rib margins. A large smooth tender liver could be palpated three fingers below the right costal margin; there was no demonstrable pulsation. No splenic enlargement could be made out, examination being hindered by a well-marked ascites. The pulse was very feeble, its rate being approximately 130 a minute with bouts of irregularity due to extrasystoles. There was no palpable thickening of the radial arteries and the blood pressure was 120/80. To percussion the heart was enlarged both to the right and to the left. The cardiac impulse was forceful and diffuse, in marked contrast to the quiet pulse. There was a systolic murmur, maximal at the apex and radiating diffusely, a loud pulmonary second sound, and then a mid-diastolic

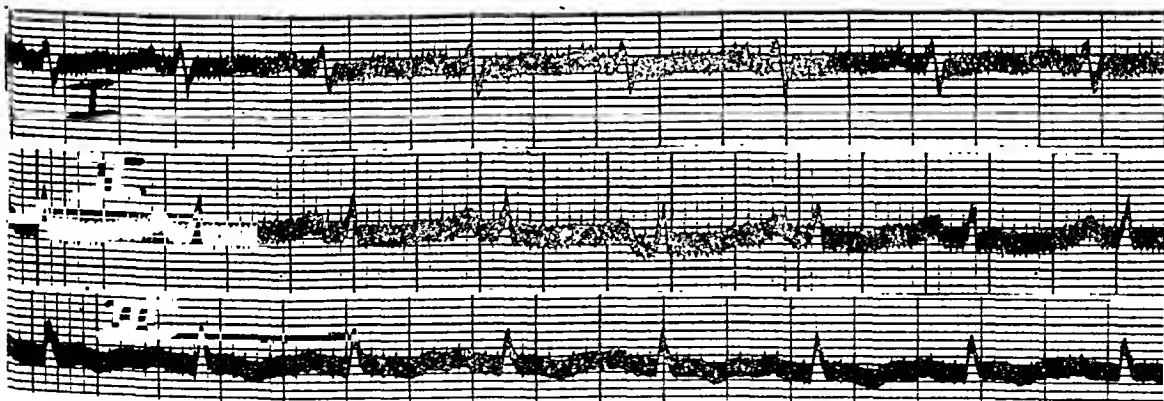


FIG. 1.—Electrocardiogram showing general low voltage response; none of the extrasystoles that were noted clinically are seen in this record.

"filling type" murmur heard best internal to the apex. The bases of both lungs were dull to percussion, and crepitations were generalized but most marked at the bases posteriorly.

On these findings a diagnosis of mitral stenosis and heart failure was made. There was no response to digitalis and diuretin, and mersalyl failed to bring about a diuresis, the œdema steadily increasing. Terminally she developed coupling and tripling of the beats and digitalis was withdrawn. During her stay she was very drowsy. A cardiogram showed general low voltage (Fig. 1); no radiological examination was possible.

On the evening of the fourth day she suddenly had an attack of intense dyspnoea and began coughing up a considerable amount of clear frothy fluid. Death occurred in about five minutes.

PATHOLOGICAL REPORT (ABSTRACT)

The body was of a well-developed and fairly well-nourished subject; there was œdema of the lower extremities. The pericardial cavity was enormously enlarged, measuring 22 cm. from apex to base, 15 cm. transversely, and 12 cm. antero-posteriorly. It contained about 150 c.c. of clear fluid. The heart was enlarged, especially on the right side, and the apex was formed by the greatly enlarged right ventricle. The right auricle was distended by 84 g. of post-mortem clot; no ante-mortem thrombi were present. The right ventricle was dilated and hypertrophied to a thickness of 0.8 cm. measured midway between the apex and the base. The dilated pulmonary ring measured 9 cm. The tricuspid and pulmonary cusps were normal. The left auricle was much dilated and largely filled by an enormous myxoma (Fig. 2). This



FIG. 2.—Photograph of the heart with the tumour in situ. The specimen is fresh and unfixed.

measured 7.5 cm. transversely, 5.9 cm. from above downwards, and was 5.5 cm. thick. It was adherent to the septal wall of the left auricle by a narrow pedicle 1 cm. in diameter. Although not actually touching it, this pedicle was attached just opposite the left edge of the foramen ovale. Except for a few small areas of white and red clot this tumour presented externally a very translucent surface partly smooth and partly rippled. There was no mitral stenosis, the valve admitting four fingers easily, and there were no ante-mortem thrombi in the auricle apart from those on the surface of the myxoma.

The myxoma had sufficient freedom to press against the left auricular wall opposite the mitral valve, where oclusion must have been very marked. Apart from this it practically filled the auricle, and only the auricular appendix and the actual mitral orifice were not filled by growth. The pulmonary veins must have been obstructed, and only one, the left inferior, seemed to have escaped obstruction by the myxoma.

The left ventricle, in contrast to the right, was short and atrophic. The heart and the myxoma weighed 450 g.

The lungs showed the induration of chronic venous congestion with an intense œdema and some recent infarcts; the right weighed 840 g., the left 650 g. The main pulmonary arteries showed slight dilatation but no atheroma. The liver had a well-marked nutmeg appearance. Other organs also showed signs of congestion and numerous infarcts of varying ages. The serous sacs contained a moderate amount of clear transudate.

Microscopically the tumour showed the appearances typical of myxoma, with long pro-

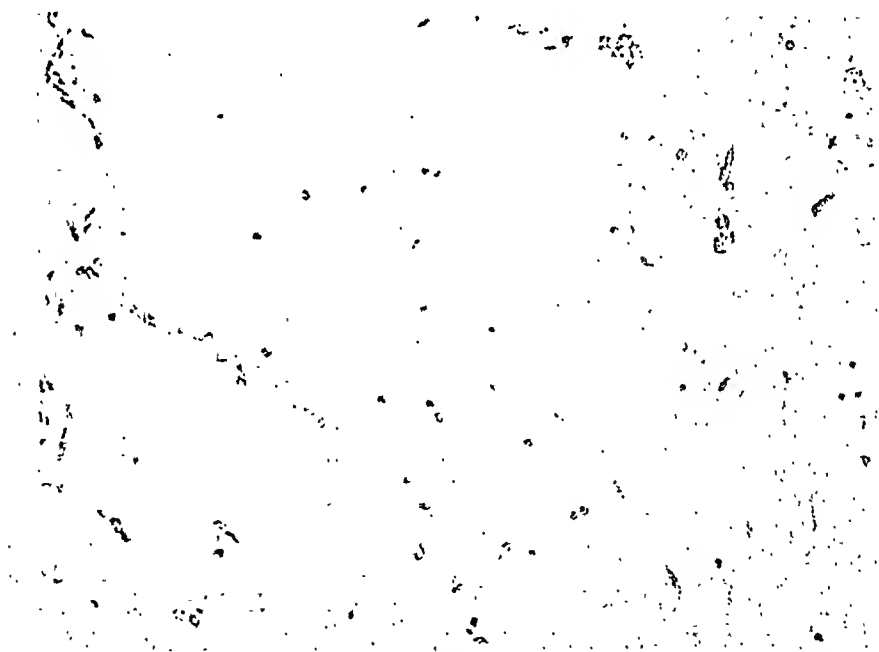


FIG. 3.—Microphotograph of a section of the tumour stained by Weigert's iron hæmatoxylin and van Gieson. Magnification $\times 180$.

cessed myxoma cells rather widely scattered in a pale staining hyaline matrix; nuclear irregularities and mitoses were not seen. It was covered by a layer of endothelium, but here and there this was lacking, being replaced by thrombus (Fig. 3). Some of these areas contained a little hæmosiderin, but elsewhere, including all the deeper parts of the tumour, there was no pigment, fibrous tissue, or other indication of organized blood clot.

COMMENT

There have been a great many arguments as to whether these cases are true tumours or organized thrombi; the papers of Hamilton-Paterson and Castleden (1942), of Fawcett and Ward (1939), and of Yater (1931) summarize these discussions. There can be little doubt

that the mass in the auricle in the present case was a true myxoma. The naked eye and microscopical appearances were of myxoma, and there was no lesion such as mitral stenosis present to account for thrombosis. There was no evidence of rheumatic infection. Again it arose from the characteristic site—the margin of the foramen ovale—where myxomatous rests have been found (Ribbert, quoted by Fawcett and Ward). There was no deep siderosis or fibrosis which would suggest that the mass was an organized thrombus.

The tumour must have been of slow growth and long duration. The chronic venous congestion was as marked as in the average case of mitral stenosis, and as the patient had cardiac symptoms a year before death the tumour must then have been large enough to cause such symptoms and the chances are that it was not then much smaller than it was at death. The infarcts in the organs in the systemic circulation were considered the result of detachment of clot from the surface of the growth; most of them were recent.

Certain of the features of this case are of interest as having been found in records of other patients with this lesion. The case of Gilchrist and Millar died suddenly as did this one, and a similar mode of death has been not infrequent in previous reports. The mechanism in this case would appear to have been a settling down of the tumour in the mitral orifice, this giving rise to a picture like acute left ventricular failure with pulmonary œdema. Other cases have been reported as being liable to attacks of paroxysmal dyspnœa. Sudden death may occur in patients with or without a previous cardiac history (Yater, 1931).

No story of postural fainting attacks or of pain was elicited. It was not noted whether any alteration in the murmurs took place with change of posture. There was no response to treatment, this being in accordance with the usual reports.

The commonest clinical diagnosis is of mitral stenosis, for the condition of auricular myxoma is so rare that it is not likely to be considered, and the picture produced by the mass obstructing auricular blood flow is very similar, in this case no doubt producing the mid-diastolic murmur. Gilchrist and Millar remark “. . . occasions may arise in the presence of heart disease of unknown ætiology, particularly if symptoms be unusual and physical signs difficult to interpret, when the diagnosis might well come to mind, perhaps most readily by a process of exclusion.”

SUMMARY

A case of myxoma of the left auricle with congestive heart failure and sudden death is presented with an autopsy report.

My thanks are due to Dr. J. G. Thomson for his kindness in giving me the use of his autopsy report, and to Dr. J. C. Spence to whose ward the case was admitted.

REFERENCES

- Fawcett, R. E. M., and Ward, E. M. (1939). *Brit. Heart J.*, 1, 249.
Gilchrist, A. R., and Millar, W. G. (1936). *Edin. med. J.*, 43, 243.
Hamilton-Paterson, J. L., and Castleden, L. I. M. (1942). *Brit. Heart J.*, 4, 103.
Yater, W. M. (1931). *Arch. intern. Med.*, 48, 627.

CIRCULATORY FAILURE DUE TO VITAMIN B DEFICIENCY

BY

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Cases of cardiac failure due to deficiency in vitamin B1 have been recognized in this country, and although the number of reported cases is small, their recognition is important since treatment by adequate doses of vitamin B1 is rapidly effective, whereas the usual methods of treatment fail. Most cases so far reported occurred in patients drinking too much alcohol and living on an inadequate diet, but a few were caused by deficient diet alone. Observations on three cases of "avitaminosis-B1 heart" showed some unusual features which seem to justify a communication. Two of the three drank too much alcohol, but in the remaining one the condition was caused solely by deficient diet.

CASE REPORTS

Case 1. A man, aged 42, was referred to me on October 25, 1939, because of a dry irritative cough of two months' duration, the bouts of coughing being precipitated by exertion and often terminated by vomiting. Other complaints were general weakness, especially in the legs, and shortness of breath, even on walking slowly on the level. Latterly intermittent swellings had occurred in various parts, especially in the face, legs, and penis; such swellings developed rather quickly, in the course of a few hours, lasted for varying periods of time, and subsided again in the course of a few hours. He "had always drunk too much," chiefly port, cheap wine, and some beer; his appetite had steadily deteriorated: a small breakfast was his only solid meal and this he often vomited.

On examination, he had a hacking, brassy cough, reminiscent of the type met in cases of mediastinal tumour or aortic aneurysm. The face was puffy and pale, and the left mandibular region was diffusely swollen. The right lobe of the thyroid was slightly enlarged. There was a regular tachycardia of 98, a short systolic murmur over the apex, and a few fine crepitations over the right base. The blood pressure was 130/85. The lower border of the liver was just palpable on deep inspiration. On the right calf were three shallow ulcers. Radiologically the heart was much enlarged to the right and left; the normal concavity on the left border was absent and the region of the pulmonary conus was slightly prominent. Hæmoglobin, 70 per cent. There was no œdema of the legs or genital organs, but when seen one week later there was marked œdema of the penis, which according to the patient had come on in the course of a few hours; there was also slight œdema of the ankles. An electrocardiogram (Fig. 1A) showed sinus tachycardia, rate 98. The main deflections in all three limb leads were directed upwards and there was a small S I and a small Q III. The T waves in lead I and the left pectoral chest lead were very wide, shallow and upright and had a dome-like appearance with their convexity directed upwards, originating in the iso-electric line in lead I and slightly (1.5 mm) above it in the chest lead; there was no high take-off. T II was almost absent and T III inverted. The duration of the electrical systole (Q-T interval) was greatly increased. It is always related to the heart rate and using the formula most commonly employed: $Q-T = K \cdot \sqrt{\text{length of cycle}}$, K (calculated in lead I) was found to be 0.49 (upper limit of normal 0.43 according to Shipley and Hallaran, 1936); the duration of Q-T was also considerably outside the normal limits of the diagram worked out by Hegglin and Holzmänn (1937) to show graphically the range of normal Q-T intervals with different heart rates.

The patient was put on vitamin B1 (Betaxan, 25 mg. by injection, daily for 4 days, and later once a week, in all 7 injections, also 20 mg. by mouth daily), and when seen again on November 15 his condition had improved. The swellings, cough, and crepitations had disappeared and the dyspnoea was considerably less. He had lost 17 lb. in three weeks. The heart shadow had decreased in size. Fig. 1B showed conspicuous changes as compared with Fig. 1A: R I had increased in height and the main deflections in lead III were now directed downwards and grossly slurred; T I had become inverted and T III upright, the R-T in lead I was curved, with the convexity directed upwards. The duration of the electrical systole had further increased, K being 0.50. Altogether the tracing showed features most commonly seen in cases of coronary disease. When seen again on December 8 the patient felt fit, and apart from the ulcers on his leg which had not quite healed, all his symptoms and

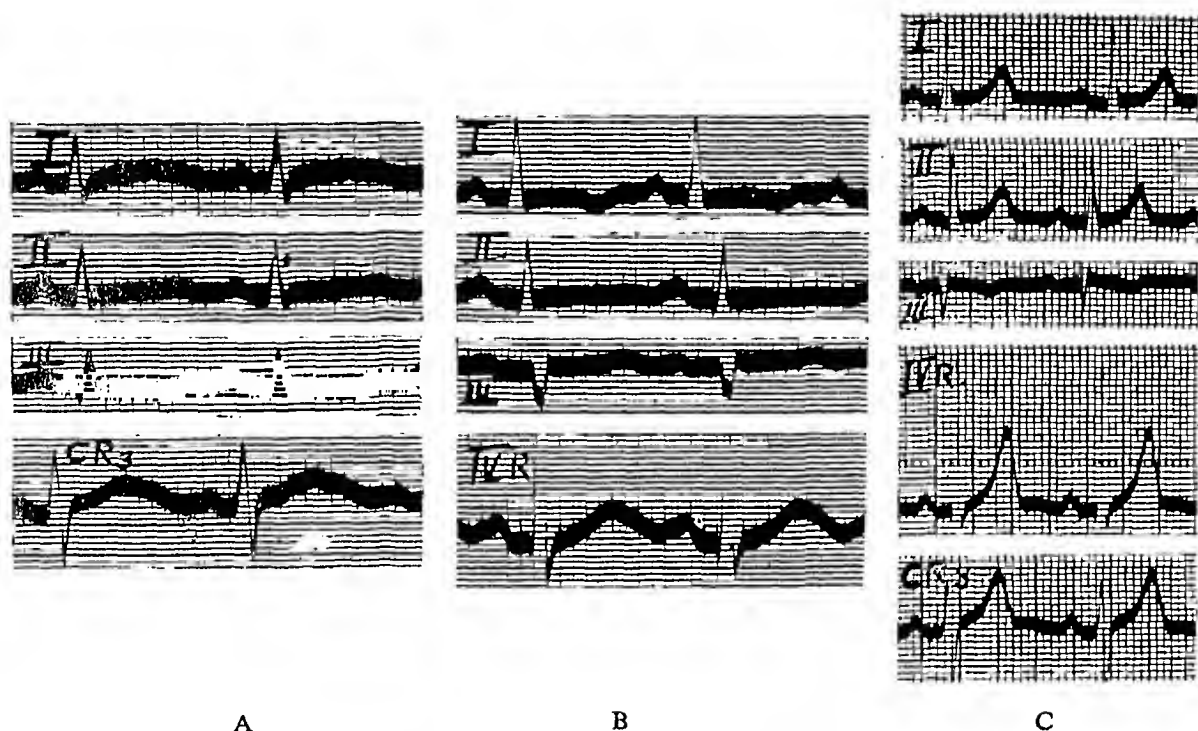


FIG. 1.—Case 1. (A) Oct. 25, 1939; (B) Nov. 15, 1939; (C) Aug. 23, 1940. Time markings in (A) and (B) 1/25 sec., in (C) 1/25 and 1/5 sec. In this and the subsequent figures: I, II, III, limb leads; IVr, right arm—apex; CR₃, right arm—fourth left intercostal space midway between left border of sternum and midclavicular line. For description of changes, see text.

signs had disappeared. A cardiogram showed a rate of 92; R II had become higher and small R waves had appeared in lead III; T I and T II were upright and normal in shape, measuring 3 and 2.5 mm. respectively; T III had decreased in height to 0.5 mm. The chest lead (apical) was normal. The duration of the electrical systole had considerably decreased, K being 0.46. The patient felt well until March, 1940, when he started to drink again heavily. He discontinued vitamin B1 in June, 1940, but took halibut liver oil and malt, and when seen again in August, 1940, complained of a continuous feeling of anxiety and slight œdema of the ankles. A cardiogram (Fig. 1C) was normal in all leads, showing some left axis deviation; the rate had decreased to 71–77. The duration of the electrical systole had become normal, K being 0.42. Subsequently, the patient discontinued all treatment in spite of drinking even more heavily. When seen again in October, 1940, his general condition had deteriorated, with increased feeling of anxiety, morning sickness, some cough and occasional paræsthesiæ in the ankles, but swellings had not recurred and the cardiogram was unchanged.

Case 2. A man, aged 62 (in 1942), had been under periodical observation since 1922 for moderate emphysema of the lungs and atherosclerosis, which were very slowly progressing. Apart from slight dyspnœa on exertion, his condition did not give rise to any complaint. There was also a congenital neurological lesion diagnosed by a neurologist as *forme fruste* of Little's disease. Apart from very occasional dysphasia and ocular disturbances, he was free from complaints and the condition had remained stationary all his life. A cardiogram in 1937 (Fig. 2A) showed sinus rhythm, rate 64; there was left axis deviation with notching of S III. T I and T II were flat but upright, the S-T intervals in lead I were normal and in lead II slightly (<1 mm.) depressed below the iso-electric line; the chest lead (left pectoral) was normal. The main physical findings in 1939 were the signs of moderate emphysema of the lungs, a long systolic murmur over the apex, some rise in blood pressure (170/100) and bilateral extensor plantar reflexes.

The patient had always taken a fair amount of whisky, but while being on a full diet did not show any signs of alcoholism or vitamin deficiency. In the autumn of 1941, however, he increased his consumption of alcohol to an average of three-quarters of a bottle a day and lived almost exclusively on carbohydrates (Ovaltine and milk puddings). When seen on February 7, 1942, he was so weak that he was unable to turn over in bed, and to sit up slowly in bed with assistance constituted a maximum effort. There was marked dyspnœa, disproportionately aggravated by talking and moving, and anorexia. A purpuric rash covered both legs and there was marked muscular fibrillation in the calves, thighs, and arms and to a lesser extent on the abdomen. The calves were tender. There was a mild conjunctivitis. The lower border of the liver was now palpable about two fingers' breadth below the costal margin. The blood pressure had dropped to 125/65. The neurological findings were unchanged with the exception of the ankle jerks which were no longer obtainable. At about the same time he started a moderate periodical pyrexia which proved to be due to an infection with *Brucella melitensis*. Hæmoglobin, 66 per cent. Urine normal. Fig. 2B showed significant changes

compared with the record taken in 1937 (Fig. 2A). There was sinus rhythm, rate 75. The initial ventricular deflections in the limb leads were considerably smaller and in lead III were directed upwards. The R-T intervals had become deformed and curved with their convexity directed upwards and in leads II and III and in the chest leads were depressed below the iso-electric line. T I had become flatter and in the remaining leads diphasic. Altogether the tracing exhibited features indicative of myocardial damage.

The patient was put on vitamin B₁ injections, 10 mg. daily, also vitamin B₁ by mouth, later supplemented by other vitamins (Medikap tablets 4 daily and Redoxon 50 mg. daily, the former being replaced later by Benerva compound tablets, 6 daily), iron (Fersolate, 6 tablets a day) and coramine (15-20 drops t.i.d.). He regained some strength very quickly, and when seen again after four days could easily turn over in bed, dyspnoea and appetite had considerably improved. The conjunctivitis

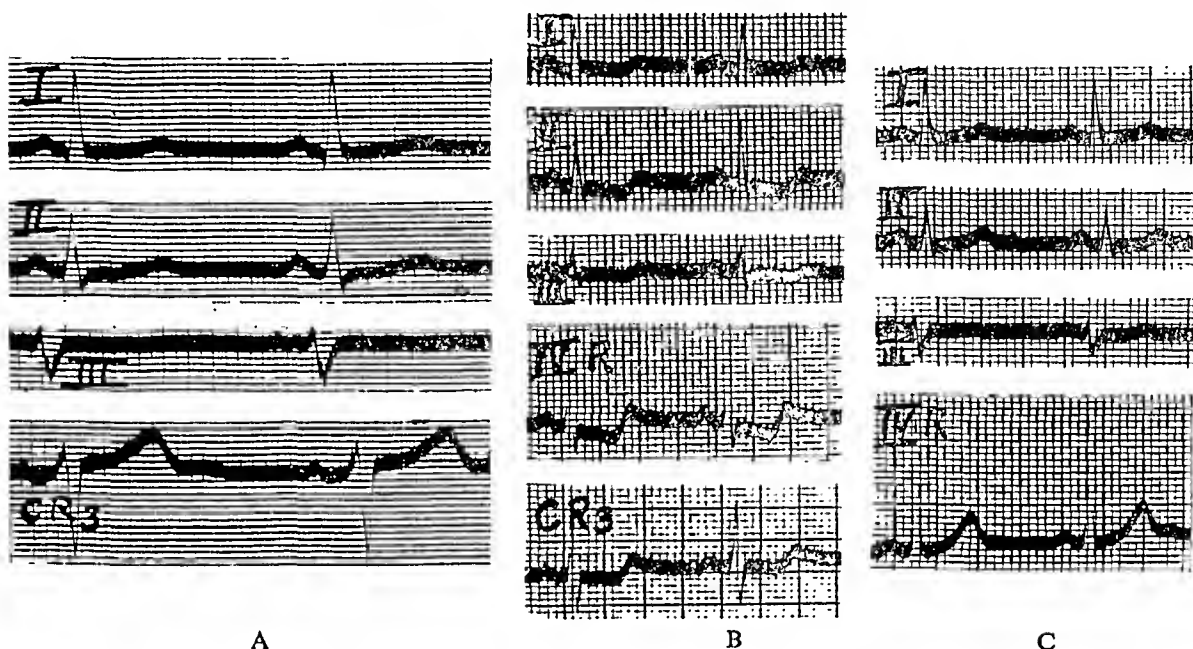


FIG. 2.—Case 2. (A) Aug. 17, 1937; (B) Feb. 7, 1942; (C) Feb. 22, 1942. Time markings: in (A) 1/25 sec. in (B) and (C) 1/25 and 1/5 sec.

had disappeared and the purpuric rash was fading. The muscular fibrillation, however, had increased in intensity and extent; it improved only very slowly, disappearing after six months, and the *Brucella* infection took about eight months to clear up. The blood count improved steadily. The further convalescence was complicated by a thrombophlebitis in the right leg. The blood pressure remained low for a year, but reached 150/80 in April, 1943, and remained at that figure.

An electrocardiogram taken on the fourth day of vitamin treatment showed that the changes in the R-T portions described above had already become less marked, particularly in leads II and III; R I had increased and R III decreased in height; the rate had decreased to 70. After another 11 days of vitamin treatment Fig. 2C showed essentially the same features as the record taken in 1937 before the onset of vitamin deficiency (Fig. 2A), only that there was now a small upright T III; otherwise the signs of myocardial disease had disappeared although the *Brucella* infection was active throughout that period and on the evening before Fig. 2C was recorded the temperature had been 101.8. This observation illustrates that the electrocardiographic changes were specifically due to the vitamin deficiency. Accurate measurements of the duration of the electrical systole were not possible in this case.

Case 3. A man, aged 51. Admitted to Guy's Hospital on July 6, 1943, because of swelling of both legs and thighs, attacks of giddiness with collapse on several occasions and shortness of breath on exertion. The condition had started three months before admission and had gradually become worse. He had been out of regular work for ten years and had lived a precarious life as a tramp, having various occupations, some of which entailed much physical exertion, and he had long periods of malnutrition, usually living on tea, bread, butter, margarine, and jam, which he obtained at coffee stalls. He did not take any alcohol.

On examination he looked frail; the skin had a slight yellowish tinge. The calves were very tender and there was oedema of both legs and thighs. The abdomen was distended and there was ascites; rales were heard over both bases. Hæmoglobin, 30 per cent; blood pressure, 140/65. The ankle jerks could not be obtained. There was achlorhydria. He was put on injections of vitamin B₁, 5 mg. daily, ordinary diet and Blaud's pills and his condition improved rapidly. His urinary output was 35 oz. on the first day of vitamin treatment and during the following four days was 689 oz.

The tenderness over the calves and the dyspnoea improved in the course of a fortnight. After a week he developed diarrhoea which stopped when Bland's pills were discontinued. From July 17, ascorbic acid (50 mg.) as well as vitamin A and D were added. On discharge on August 19 to a convalescent home he was free from symptoms.

Fig. 3A was taken on the fourth day of vitamin treatment and showed sinus rhythm, rate 87. The initial ventricular deflections in all standard leads were small, R I measuring 5 and R II 4 mm, and

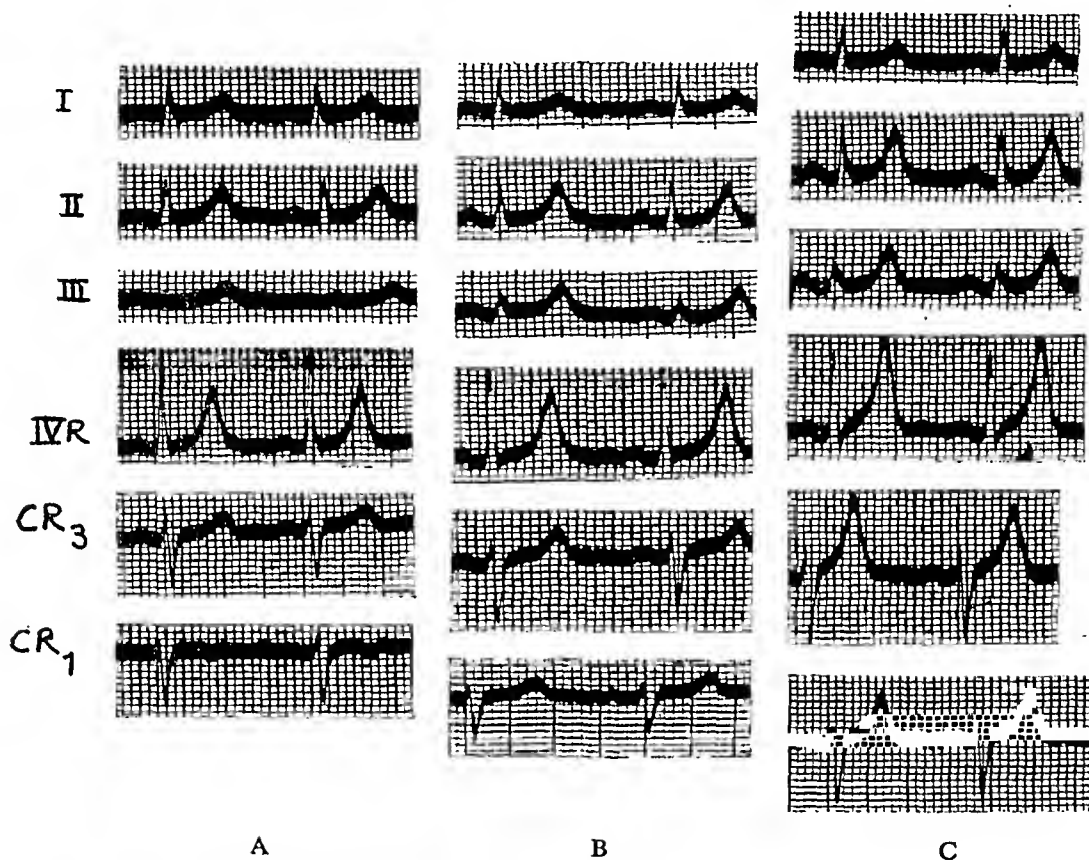


FIG. 3.—Case 3. (A) July 10, 1943; (B) July 13, 1943; (C) July 23, 1943. CR₁: right arm—right border of sternum at the insertion of the fourth rib. Time markings: 1/25 and 1/5 sec.

R III being almost invisible. In the right pectoral chest lead the T waves were inverted, otherwise the chest leads were normal. Fig. 3B, taken three days later, showed a rate of 77 and a marked increase in the height of R III and especially of T II and T III; in the right pectoral chest lead the T waves had become upright. Three days later these changes had become more marked, and a week after that there was another conspicuous increase in the height of the T waves in all the leads (except lead I) (Fig. 3C); in lead III and the apical chest lead the height of the T waves exceeded that of the R waves and in lead II they were equal in height. After another week the height of R III and of T II and T III and of the apical chest lead had decreased, and ten days later the record had remained unchanged, except that R III had become almost invisible and there was a small downward deflection instead, measuring less than 0.5 mm. The duration of the electrical systole was within normal limits throughout.

DISCUSSION

Each of the three cases showed some unusual features of general clinical or cardiological interest.

In Case 1 the outstanding symptoms were weakness, dyspnoea, a dry hacking brassy cough, and transient swellings of unusual distribution. Although a cough of this kind is known to occur in cases of vitamin B1 deficiency (Weiss and Wilkins, 1936, 1937) one does not usually associate it with this condition. Oedema of a similar distribution has been observed by Jones and Bramwell (1939), but is not usually of such transient character. In regard to the electrocardiogram, the T waves in leads I and the chest lead were unusually wide and at the same time flat and "dome-shaped" without a high take-off, the duration of the electrical

systole being markedly increased. A somewhat similar shape was found by Boyd Campbell and Allison (1940), and Weiss and Wilkins (1936, Fig. 3), but apparently is uncommon. The temporary inversion of the final deflections during the early stages of treatment with vitamin B1 has been reported by several authors (Boyd Campbell and Allison, 1940; Dustin Weyler, and Roberts, 1939; Weiss and Wilkins, 1936, 1937). Failure to recognize this as a temporary occurrence during vitamin treatment may result in a mistaken diagnosis of coronary disease, or even recent coronary occlusion. When subsequently the patient had a relapse and several clinical symptoms and signs of vitamin deficiency recurred the electrocardiogram remained normal. These observations are in keeping with the experimental findings of Weiss, Haynes, and Zoll (1938) that in rats fed on a vitamin B1 deficient diet temporary inversion of T occurred after the injection of vitamin B1 in some animals and that on repeated induction of vitamin B1 deficiency the cardiographic changes were not always identical. In dogs electrocardiographic changes were demonstrated by de Soldati (1940). Lengthening of the duration of the Q-T intervals in cases of vitamin B1 deficiency and a return to normal with adequate treatment was found by several authors (Dustin, Weyler, and Roberts, 1939; Goodhart and Joliffe, 1938; Weiss, 1940; Weiss and Wilkins, 1936, 1937; Dustin, Weyler, and Roberts, 1939), moreover, observed temporary increase at the beginning of treatment.

In Case 2 the onset of signs of vitamin B1 deficiency coincided with the onset of a *Brucella* infection. It is known that infections not infrequently precipitate the signs of beriberi which until then had remained latent (Aalsmeer and Wenckebach, 1929; Weiss, 1940). In the present case several factors known to precipitate the clinical manifestations of vitamin deficiency co-existed: a negligible intake of vitamin B1 due to gross dietary deficiency, and a high demand of this vitamin owing to the disproportionate amount of carbohydrate in the diet, the excessive consumption of alcohol, and the infection. Gross muscular fibrillation was a prominent sign and it is difficult to decide whether this was due to the vitamin deficiency, the *Brucella* infection, or the combination of the two. It disappeared after about six months of continual vitamin treatment, about two months before the last manifestation of the *Brucella* infection. Another conspicuous feature was marked dyspnoea at rest disproportionately aggravated by the slightest physical exertion. The circulatory factors responsible for this condition have been studied in detail by Hayasaki and Inawashiro (1928).

In Case 3 cardiac failure due to vitamin B1 deficiency occurred in a patient who did not take any alcohol, as a result of deficient diet only. Few such cases have been reported in this country (Konstam and Sinclair, 1940; Swan and Lewis, 1940; result of deficient absorption, Ungley, 1939). Physical exertion seems to have precipitated the onset; the importance of this factor is shown by the fact that cardiac failure is less likely to develop or is delayed in its onset in beriberi patients with paralysis (Keefer, 1930), and that severe polyneuritis is usually associated with only a mild degree of congestive circulatory failure (Weiss, 1940). Similar observations have also been made in experimental animals (Swank and Bessey, 1942; Swank, Porter, and Yeomans, 1941). The electrocardiographic findings in Case 3 resemble those of Katz (1941, Fig. 210), especially in respect of temporary gross increase in the height of the T waves in the chest lead.

It is noteworthy that in all three cases the chest leads showed changes, whereas in a series of six cases Dustin, Weyler, and Roberts (1939), found that the chest lead generally showed little disturbance. Changes in the chest leads seem to be more common in pellagra (Feil, 1936).

SUMMARY

Three cases of circulatory disturbances due to vitamin B1 deficiency are described with special reference to some unusual clinical and electrocardiographic features. Two of the three patients took an excessive amount of alcohol, in the third case the condition was caused by deficient diet only. All responded to treatment with vitamin B1.

I wish to thank Dr. Geoffrey Marshall, under whose charge Case 3 was admitted to Guy's Hospital, for his permission to examine this patient and publish his notes.

REFERENCES

- Aalsmeer, W. C., and Wenckebach, K. F. (1929). *Wien Arch. inn. Med.*, **16**, 193.
 Boyd Campbell, S. B., and Allison, R. S. (1940). *Lancet*, **i**, 738.
 Dustin, C. C., Weyler, H., and Roberts, C. P. (1939). *New Engl. J. Med.*, **220**, 15.
 Feil, H. (1936). *Amer. Heart J.*, **11**, 173.
 Goodhart, R., and Joliffe, N. (1938). *Ibid.*, **15**, 569.
 Hayasaka, E., and Inawashiro, R. (1928). *Tohoku J. Exp. Med.*, **12**, 29.
 Hegglin, R., and Holzmänn, M. (1937). *Z. klin. Med.*, **132**, 1.
 Jones, A. M., and Bramwell, C. (1939). *Brit. Heart J.*, **1**, 187.
 Katz, L. N., *Electrocardiography*. London, H. Kimpton, 1941.
 Keefer, C. S. (1930). *Arch. intern. Med.*, **45**, 1.
 Konstam, G., and Sinclair, H. M. (1940). *Brit. Heart J.*, **2**, 231.
 Shipley, R. A., and Hallaran, W. R. (1936). *Amer. Heart J.*, **11**, 325.
 de Soldati, L. (1940). *Cpt. rend. Soc. Biol.*, **133**, 323. Los trastornos circulatorios en la Avitaminosis B 1. Buenos Aires, El Ateneo, 1940.
 Swan, W. G. A., and Lewis, F. (1940). *Brit. Heart J.*, **2**, 241.
 Swank, R. L., and Bessey, O. A. (1942). *Arch. intern. Med.*, **70**, 763.
 Swank, R. L., Porter, R. R., and Yeomans, A. (1941). *Amer. Heart J.*, **22**, 154.
 Ungley, C. C. (1939). *Newcastle med. J.*, **19**, 43.
 Weiss, S. (1940). *J. Amer. med. Ass.*, **115**, 832.
 Weiss, S., Haynes, F. W., and Zoll, O. M. (1938). *Amer. Heart J.*, **15**, 206.
 Weiss, S., and Wilkins, R. W. (1936). *Trans. Ass. Amer. Phys.*, **51**, 341.
 ——— (1937). *Ann. intern. Med.*, **11**, 104.

CARDIAC OUTPUT IN MAN BY A DIRECT FICK METHOD

EFFECTS OF POSTURE, VENOUS PRESSURE CHANGE, ATROPINE, AND ADRENALINE

BY

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I. EFFECTS OF POSTURE AND VENOUS PRESSURE CHANGE

In the Fick method of estimating cardiac output (C.O.), where C.O. (litres/min.) = oxygen consumption (c.c./min.) divided by arterio-venous oxygen difference (c.c./litre), the measurement of the numerator can easily be made by spirometric methods. Hitherto the measurement of the arterio-venous oxygen difference in man by respiratory techniques has proved difficult and laborious, and it has not been possible to make frequent serial observations. The difficulties seem to be largely overcome by the method of cardiac catheterization first introduced by Forsmann (1929) and developed by Cournand and Ranges (1941). Over 394 catheterizations can now be recorded without any accidents (Forsmann (1), de Carvalho and Moniz (48), Ameuille *et al.* (60+), Cournand *et al.* (150) and the present authors (135)). The catheter has been left *in situ* as long as 24 hours (Cournand *et al.*), but the present authors have limited the period to one hour in normal subjects. Clotting does not occur on the unwettable surface of the catheter, and a slow drip of 3.8 per cent sodium citrate through the catheter prevents any thrombus formation round the hole at the tip.

METHOD

The observations were made on normal male volunteers about two hours after the midday meal. The subjects were supine, except where otherwise stated. A No. 12 radio-opaque ureteric catheter was introduced through a wide bore needle into the medial antecubital vein of the left arm. The introduction was painless. Usually the catheter passed smoothly into the right auricle where its position was verified by X-ray. In about one subject in seven an obstruction was encountered at the root of the neck, but gentle manipulation may allow passing the catheter to the desired position. Occasionally the catheter took an acute turn up into the left internal jugular vein. The catheter was attached to a citrate manometer which recorded changes in pressure in the right auricle and served to keep the catheter clear of blood; 15 c.c. samples of right auricular blood were withdrawn under oil for estimation of oxygen unsaturation. No accidents or complications have followed this procedure except sometimes an inch or so of thrombosis near the point of insertion in the arm vein.

Oxygen unsaturation of right auricular blood was estimated in a Haldane blood gas apparatus modified to take 6 c.c. samples. The oxygen capacity was estimated by haemoglobinometry. When the lungs were normal a value of 95 per cent saturation was assumed for arterial blood and the arterio-venous oxygen difference calculated from this assumption. The estimation of oxygen unsaturation was made at room temperature, at which the oxygen consumption was also measured by a Benedict spirometer. This simplifies the calculation considerably. The arterio-venous oxygen differences quoted below are uncorrected for N.T.P.

In the recumbent position the mean right auricular pressure (R.A.P.) is recorded with the posterior surface of the thorax equal to zero level. The pressure averages approximately 14 cm. anterior to this point (Richards *et al.* 1942).

RESULTS

Normal values.—As will be demonstrated in the second section, heart rate influences resting output, and for this reason we tabulate as “normal” values in which the pulse rate was under 80 per minute. Numbers are as yet too few to establish a statistical mean and range, and data may conveniently be grouped as follows:—

| TABLE I | |
|---|--------|
| Arterio-venous oxygen difference (c.c./litre) | Number |
| 30-40 | 3 |
| 40-50 | 10 |
| 50-60 | 4 |

Cournand *et al.* (1943) give a mean figure of 45 c.c./litre for the arterio-venous oxygen difference. Baumann (1930) by heart puncture got an average figure of 51·5 c.c./litre.

Posture. In 17 subjects the cardiac output was estimated in the erect and supine positions. Samples were taken while subjects were standing quietly immediately after X-ray screening. The actual oxygen consumption in this position was not measured, but previous data (McMichael, 1937; Grollman, 1932; Nylin, 1934) indicate the average value to be 14 per cent over the recumbent oxygen consumption rate. Results are shown in Table II. It is seen that cardiac output increases by an average of 33 per cent on lying down. This agrees with the bulk of previous work (see Hellebrandt and Franseen (1943) for references) and refutes the recent suggestion of Starr and Rawson (1941), based on the ballisto-cardiograph, that there is no change.

TABLE II
POSTURAL CHANGES IN ARTERIO-VEINUS O₂ DIFFERENCE
(14 subjects)

| | | | | | | | | | | | | | | | | | |
|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|-------------|
| Arterio-venous O ₂ difference (c.c./litre) | Recumbent | .. | 45 | 30 | 34 | 42 | 52 | 42 | 36 | 30 | 42 | 46 | 41 | 44 | 34 | 40. | Average: 40 |
| | Standing | .. | 60 | 66 | 53 | 70 | 65 | 49 | 62 | 43 | 75 | 57 | 61 | 72 | 53 | 65 | Average: 61 |
| | Average O ₂ consumption c.c./min. .. Recumbent: 240. Standing: 274 | | | | | | | | | | | | | | | | |
| | Cardiac output/min. Recumbent: 6 litres. Standing: 4·5 litres | | | | | | | | | | | | | | | | |

Change in right auricular pressure. The venous pressure can be conveniently raised by intravenous infusions of saline (Sharpey-Schafer and Wallace, 1942) and lowered by venesection (Wallace and Sharpey-Schafer, 1941) or by cuffs on the thighs at diastolic blood pressure. Sample data from observations of these types are shown in Fig. 1, 2, and 3, and

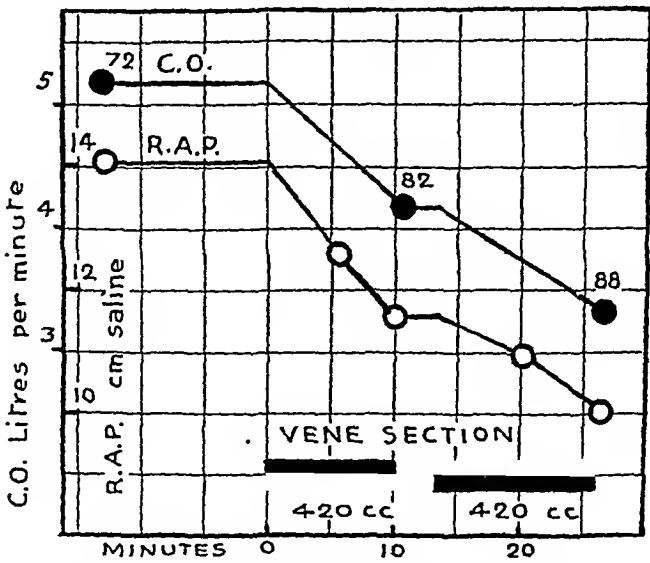


FIG. 1.—Effect of venesection on cardiac output and right auricular pressure. In Fig. 1, 2, and 3 figures beside cardiac output determinations indicate heart rate. Right auricular pressure (R.A.P.) and cardiac output (C.O.) fall in parallel.

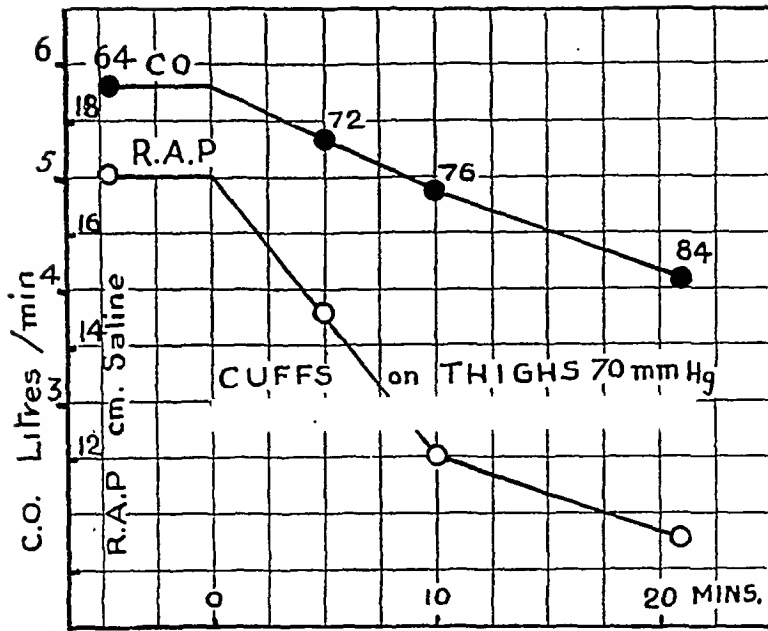


FIG. 2.—Effect of tourniquets on both legs at 70 mm. Hg. Blood is trapped in the leg veins, right auricular pressure (R.A.P.) and cardiac output (C.O.) falling together.

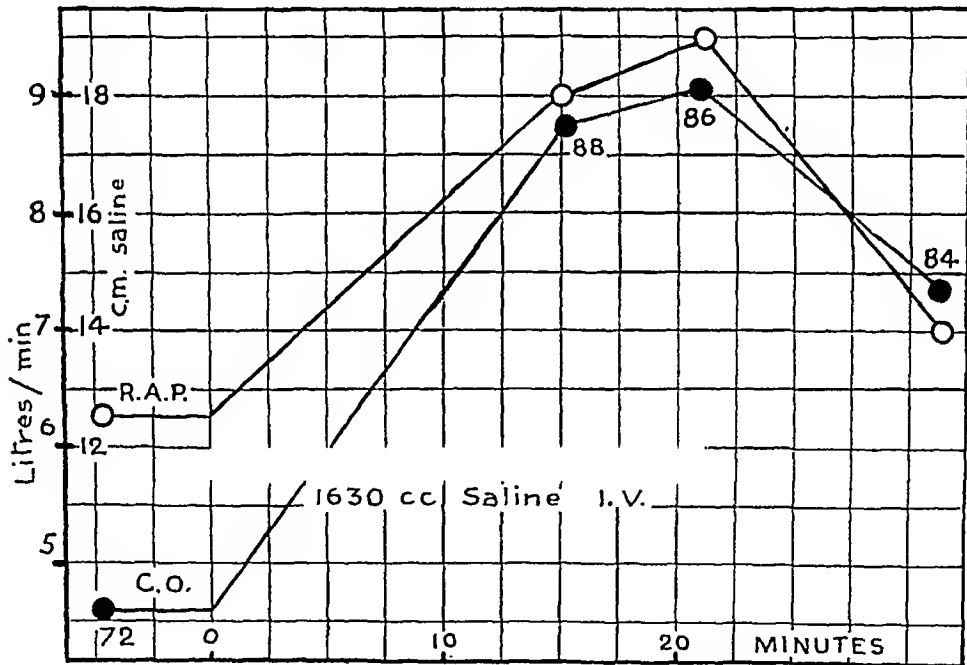


FIG. 3.—Effect of raising right auricular pressure (R.A.P.) by saline infusion. During infusion the cardiac output (C.O.) rises. On stopping the infusion saline is lost from the circulation and right auricular pressure and cardiac output fall together.

the collected data from all observations are shown in Fig. 4. As expected from Starling's law of the heart, a reduction in right auricular pressure leads to a fall in cardiac output, while a rise is accompanied by an increase.

DISCUSSION

Taking all our available data into account, the average normal resting cardiac output in the recumbent position is (240/45) 5.3 litres a minute, while in the standing position it is 25 per cent less, i.e. 4 litres. These are higher than figures previously obtained by the

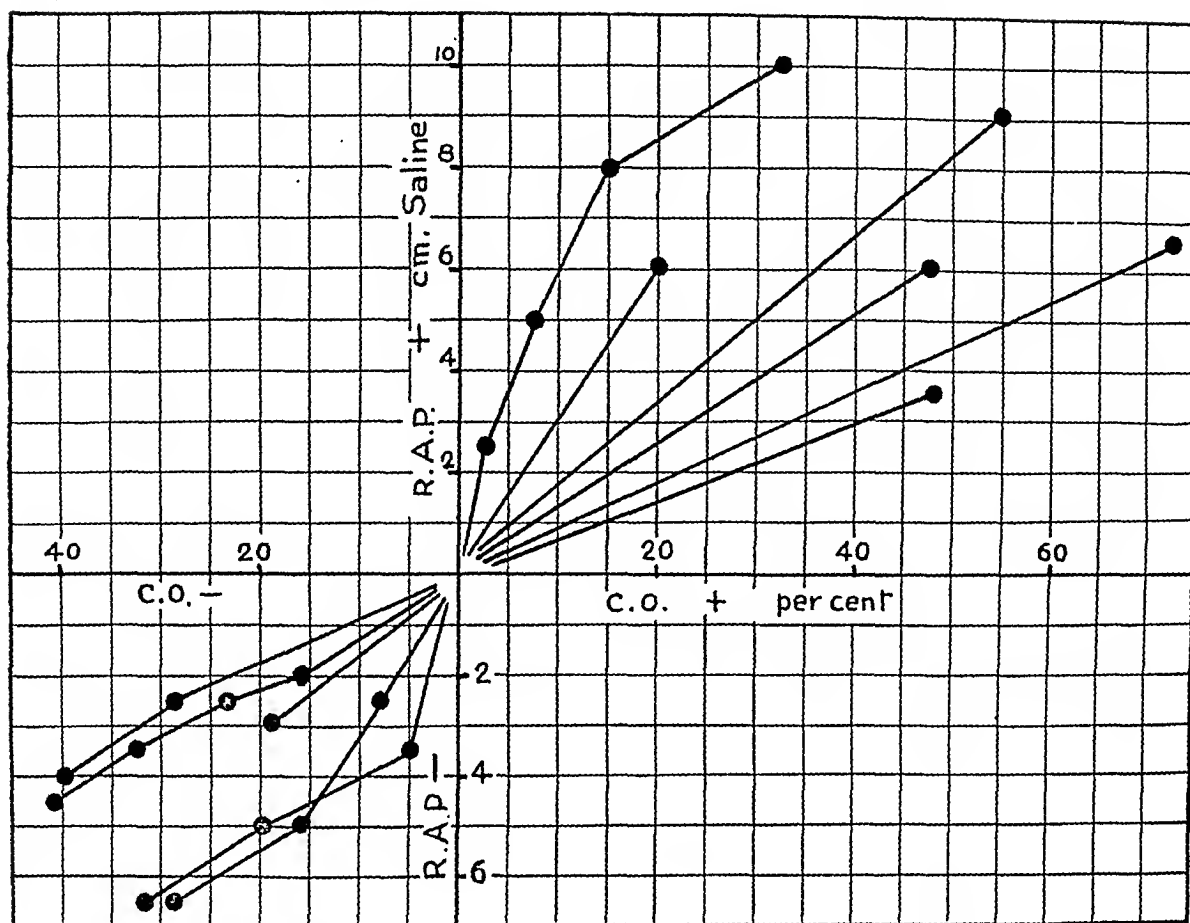


FIG. 4.—Collected data in 11 subjects showing increasing cardiac output (C.O.) with intravenous infusion and decrease with venesection or cuffs on legs.

acetylene technique, which gave an average cardiac output in the recumbent position of 4 litres a minute (McMichael, 1937): it is of interest, however, that two techniques then used gave an average increase in cardiac output of 32 per cent and 38 per cent in recumbency, which compares well with 33 per cent by the new method. Relative changes seem to have been fairly accurately reflected, but the absolute values were subject to a systematic error.

The assumption of 95 per cent arterial oxygen saturation in these observations may be criticized. Our aim has been to simplify the technique as much as possible for application to clinical problems, and *repeated* arterial punctures do not seem to be justified. For following *changes* in any individual under test the assumption can lead to little significant error. A range of 93–97 per cent oxygen saturation of arterial blood would give a standard error of 2 c.c. per litre in the arterio-venous oxygen differences.

II. EFFECTS OF ATROPINE, ADRENALINE, AND HEART RATE

The methods and conditions of study were the same as in the first part.

Atropine. Observations were made in 10 subjects. Two main effects were found. Raising the heart rate increased cardiac output in all subjects except two, and there was a fall in right auricular pressure (R.A.P.) in all (Fig. 5). Atropine was given intravenously in doses of 1 mg. and the usual sequence of events was as follows: within 30 seconds the heart rate was increasing, reaching its maximum rate in about 1–2 minutes; at this point the cardiac output was considerably increased; the R.A.P. fall was slower in appearing and only attained a steady level after a few minutes. Fig. 6 shows that this fall in right auricular pressure may be accompanied by a decrease in cardiac output from the high level attained

earlier by atropine. In two out of ten observations no rise in cardiac output was observed at the time of sampling. It would appear that a large fall in R.A.P. was sufficient to prevent

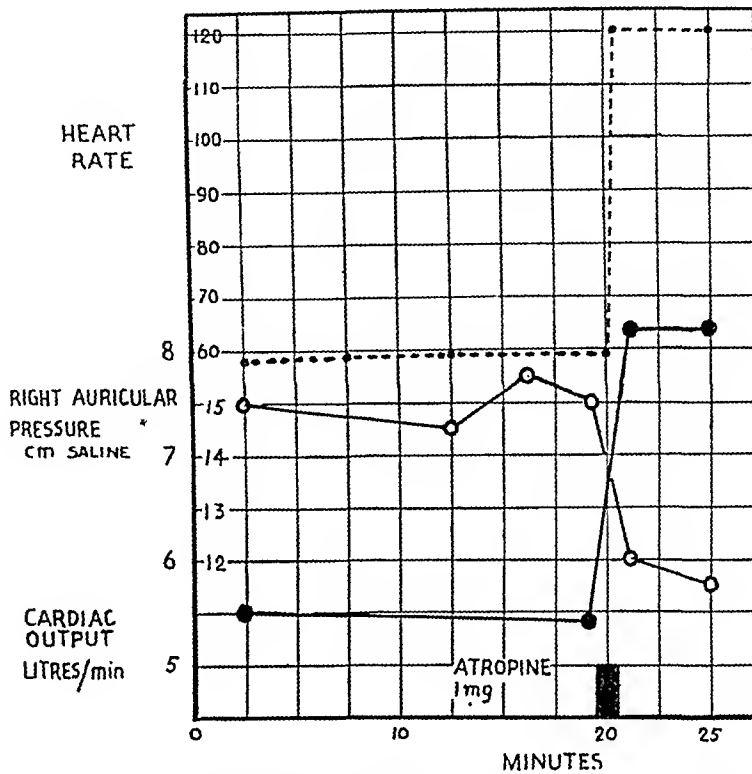


FIG. 5.—Usual immediate response to intravenous atropine. Heart rate and cardiac output increase, right auricular pressure falls.

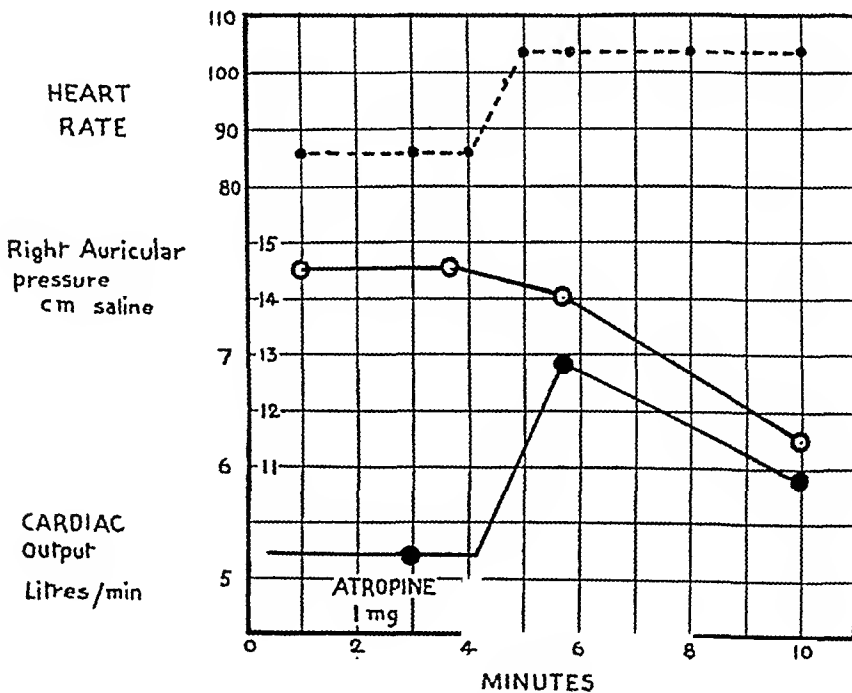


FIG. 6.—Showing initial increase in cardiac output after atropine followed by a fall as right auricular pressure decreases.

the usual rise of cardiac with atropine acceleration (Fig. 7). These results indicate that the effects of acceleration of the heart rate increasing cardiac output may be modified by venous pressure changes.

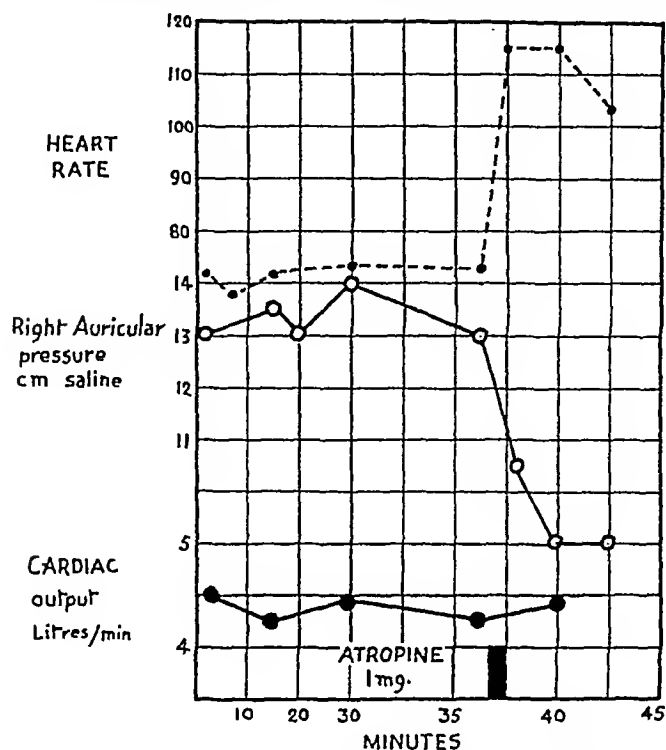


FIG. 7.—Showing no increase in cardiac output after atropine with considerable fall in right auricular pressure.

Adrenaline. We studied the effects of doses that, infused intravenously, did not raise the blood pressure or increase the heart rate. Such doses were under $10\mu\text{g}$. a minute, but the suitable dose for each individual may have to be found by trial. Dilatation of muscle vessels is produced by adrenaline administered in this dosage, and in some experiments this

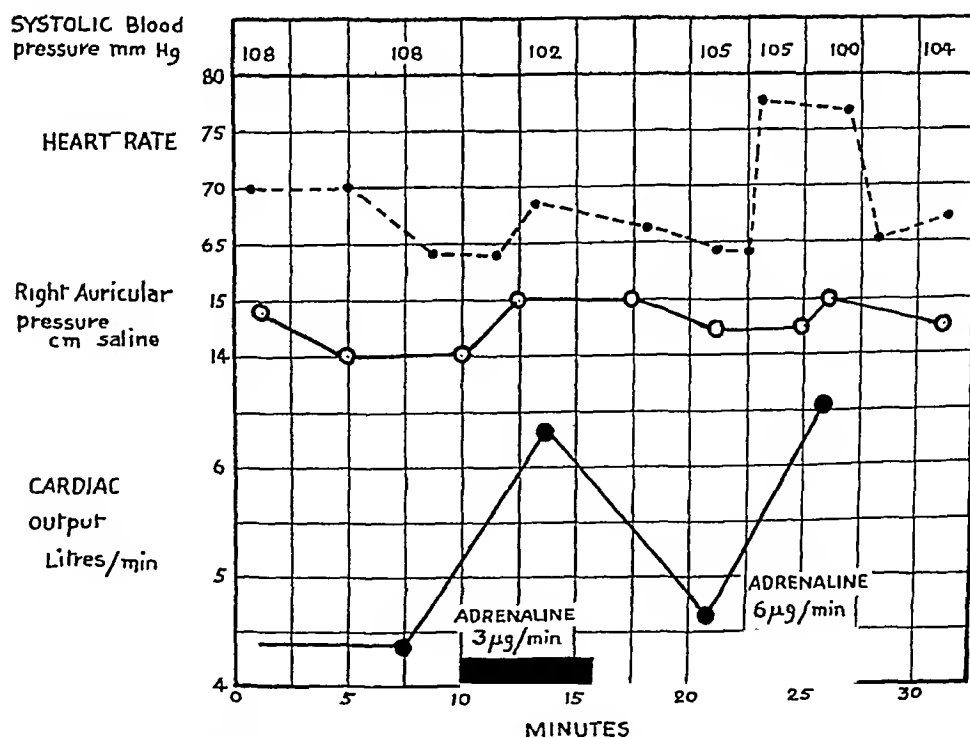


FIG. 8.—Effect of adrenaline infusion at $3\mu\text{g}$. a minute. Cardiac output increases without change in heart rate or right auricular pressure or rise in blood pressure. When the dose of adrenaline was doubled, the heart rate increased.

effect was demonstrated by Professor H. Barcroft and Dr. O. G. Edholm, who simultaneously measured forearm flow with a Lewis-Grant plethysmograph. In all of 5 subjects adrenaline increased cardiac output, and a typical observation is shown in Fig. 8. On stopping the infusion, cardiac output returned rapidly to the resting level. Slight pallor of the face was observed during infusion, and some subjects became conscious of the beating of their hearts. Conspicuous flushing of the face appeared when the infusion was stopped. The results show that adrenaline can increase cardiac output without a change in venous pressure or heart rate.

Heart rate. The total data on cardiac output determinations in normal subjects are shown plotted against heart rate in Fig. 9. The majority lie between 4 and 6 litres a minute, while

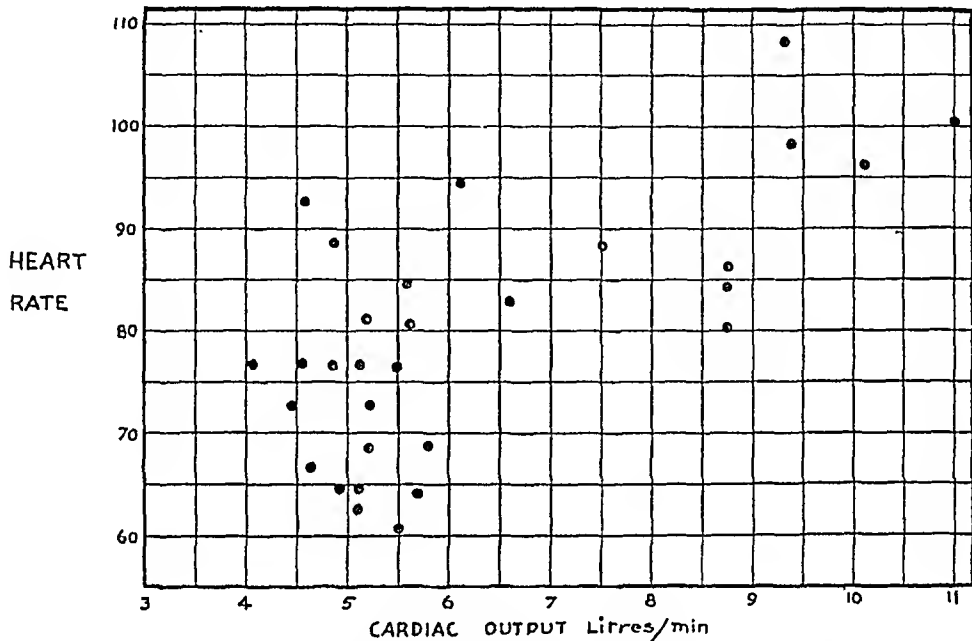


FIG. 9.—Collected data of cardiac output plotted against heart rate in normal resting males in the supine posture. The few with higher outputs show faster heart rates.

a few have higher outputs up to 10 or 11 litres a minute. It will be seen that the latter group tends to have faster heart rates, and this may be one factor in causing increased output. Other possible factors such as secretion of adrenaline or slightly increased venous pressure could not be compared from subject to subject. All those with increased output were in the younger age groups (under 40), when the circulation might be expected to be more labile.

DISCUSSION

There is a mass of physiological evidence that right auricular pressure, determining tension and length of myocardial fibres, is the major factor altering the output of the heart provided the rate remains constant. The first part of this work shows such effects in man, although rate and other factors for obvious reasons could not be controlled.

Wiggers (1938) indicates that within the usual physiological range increased rate leads to increased minute output so long as the venous pressure is kept constant. We have as yet no explanation to offer for the fall in right auricular pressure observed so often after atropine. Its late onset indicates that it may be a physiological adjustment secondary to the initial increase in output.

Independently of rate and right auricular pressure, the adrenaline effects indicate yet another mechanism controlling cardiac output. Adrenalin produces increased systolic ejection at the same mean filling pressure in the right auricle. This is in accordance with the observation of Wiggers (1927) that adrenaline causes a stronger and more rapid ventricular contraction and also a more complete relaxation in diastole.

SUMMARY

Serial estimations of cardiac output and right auricular pressure can be made by means of a ureteric catheter passed along the veins into the right auricle.

Normal resting values for arterio-venous oxygen differences were rather lower than those obtained previously by the acetylene method.

Cardiac output in the supine posture showed a 33 per cent increase over that in the erect.

A fall in right auricular pressure reduced, and a rise in right auricular pressure increased, the cardiac output.

Acceleration of the heart with atropine usually increased cardiac output and caused a fall in right auricular pressure. Occasionally the fall in right auricular pressure may operate against an increase in cardiac output.

Intravenous adrenaline increased cardiac output in doses that did not accelerate the heart or raise the blood pressure.

Normal subjects with high resting outputs had faster heart rates than the others.

We wish to thank the volunteers from the Friends Ambulance Unit. The Medical Research Council defrayed our expenses.

We are indebted to the staff of the Radiological Department and to Mr. A. H. Latham for their technical aid.

REFERENCES

- Ameuille, P., Ronneaux, G., Hinault, V., Desgrez, —, and Lemoine, J. M. (1936). *Bull. Mém. Soc. méd. Hop.*, Paris, 60, 729.
- Baumann, H. (1930). *Verh. dtsch. Ges. inn. Med.*, 42, 247.
- Cournand, A., and Ranges, H. A. (1941). *Proc. Soc. exp. Biol. N.Y.*, 46, 462.
- Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lauson, H. D., Gregersen, M. I., and Richards, D. W. (1943). *Surgery*, 13, 964.
- de Carvalho, L. and Moniz, E. (1933). *Acta Radul.*, 14, 431.
- Forssmann, W. (1929). *Klin. Wschr.*, 8, 2085.
- Grollman, A. (1932). *The Cardiac Output of Man in Health and Disease*, Springfield, Illinois, C. C. Thomas.
- Hellebrandt, F. A., and Franseen, E. B. (1943). *Physiol. Rev.*, 23, 220.
- McMichael, J. (1937). *Quart. J. exp. Physiol.*, 27, 55.
- Nylin, G. (1934). *Skand. Arch. Physiol.*, 59, 237.
- Richards, D. W., Cournand, A., Darling, R. C., Gillespie, W. H., and Balwin, E. D. (1942). *Amer. J. Physiol.*, 136, 115.
- Sharpey-Schafer, E. P., and Wallace, J. (1942). *Brit. med. J.*, 2, 304.
- Starr, I., and Rawson, A. J. (1941). *Amer. J. Physiol.*, 134, 463.
- Wallace, J., and Sharpey-Schafer, E. P. (1941). *Lancet*, 2, 393.
- Wiggers, C. J. (1938). *Physiology in Health and Disease*, 2nd edit.
- (1927). *J. Pharm. exp. Ther.*, 30, 233.

THE HEART IN MYOTONIA ATROPHICA

BY

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Myotonia atrophica is a familial complaint appearing in young adult life. Atrophy of muscles is conjoined with increased tone. Early baldness, with wasting of the temporal, facial, and sterno-mastoid muscles when the disease is fully developed, give to the patient a characteristic appearance (Fig. 1). Atrophy also takes place in the girdle and limb muscles.

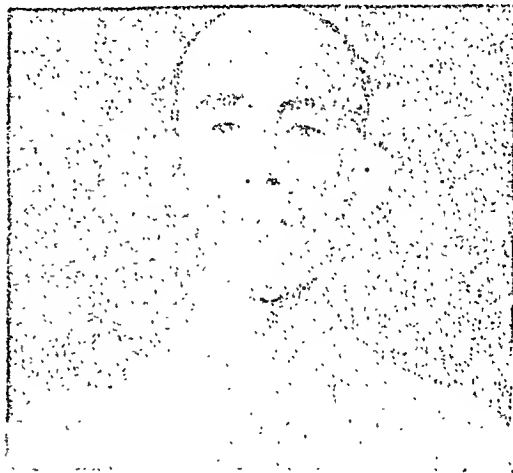
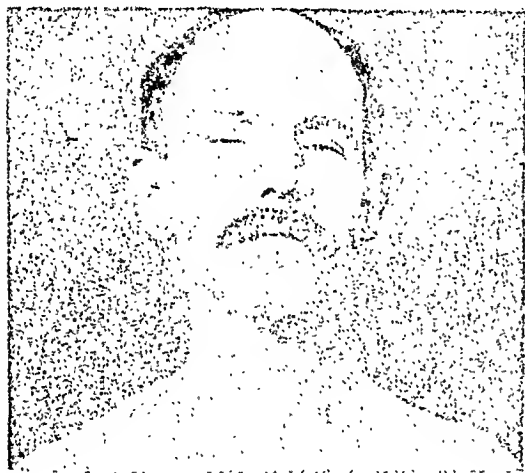


FIG. 1.—Two patients (Cases 7 and 13) showing characteristic features of myotonia atrophica.

Increased tone is illustrated by the delayed relaxation of the hand-grip, by dimpling of the tongue when struck by a spatula or by a patella hammer against the lower teeth, and by the adduction jerk of the thumb when the thenar eminence is struck. Cataract (seen only by the slit-lamp during the early years of the disease) and atrophy of the testes with impotence are other characteristic findings. The condition is not uncommon, but because such obvious changes are absent during the early stages of the illness, it may go unrecognized for many years. The medical history of patients in whom I examined the heart convinced me of the need to implement the myopathic signs with others that might lead to an earlier diagnosis and spare the patients the unfair judgment passed on them by employers and doctors alike in regarding them often as nervous subjects or even malingerers. I found that signs discovered during the examination of the cardiovascular system contribute to the surer and earlier diagnosis of myotonia atrophica.

In the English literature dealing with myotonia there is little reference to its effects on the heart. Adie and Greenfield (1923) described 20 cases and mentioned that in one examined at necropsy the heart was healthy and in another the electrocardiogram was normal; this led them to say that the observation of the heart being affected in myotonia lacked confirmation. It was Maas and Zondek (1920) who first wrote about involvement of the heart,

reporting cardiac enlargement in one case which also showed sinus bradycardia and a prolonged P-R interval, and similar changes in the cardiogram of two other patients. In seven patients examined by Guillain and Rouquès (1932) the P-R period was slightly prolonged in two only. Sinus bradycardia was the only change noticed by Havier and Decourt (1933) in one case, but in another reported by Mondon and Pasquet (1939) the P-R interval was long and the T wave was inverted in lead I. Two out of three young patients with myotonia described by Carrillo (1941) had abnormal cardiograms, showing low voltage of the P wave, long P-R interval, wide and notched QRS complex, and left axis deviation. Segura and Lanari (1941), on the other hand, described eleven patients with different forms of myotonia in whom clinical, cardiographic, and radiological examination had shown no abnormality of the heart, while microscopy in one instance demonstrated a healthy myocardium.

In order to test these different opinions on the state of the heart in myotonia atrophica, thirteen cases were collected for special examination. Ten were males and three females. Their ages varied from 23 to 45 and the average age was 35 years. Each had been diagnosed by a neurologist as a typical case of myotonia atrophica.

Cardiac symptoms. The most prominent symptoms were always those identified with the myopathy. Two patients (Cases 12 and 13), in whom the heart was enlarged, complained of breathlessness but neither showed signs of heart failure. Two attacks of unconsciousness in one patient (Case 12) had the features of Stokes-Adams attacks although they were not directly observed. None complained of heart pain.

The pulse. In only two cases was the pulse slow and in one of these the sinus bradycardia alternated with heart block. The force of the pulse was often noticeably small and this change was so common (8 out of 13) as to suggest that it is a characteristic sign in myotonia atrophica.

The blood pressure. The blood pressure was not raised in any of the 13 cases. It was highest (160/70) in Case 13 during periods of 2 : 1 heart block. In five it was low and in three of these the systolic pressure was 95 or under (see Table I). In one case administration of desoxycorticosterone acetate raised the blood pressure and this effect is shown in Fig. 2. It is not maintained that this is a specific effect in myotonia atrophica and there was no change

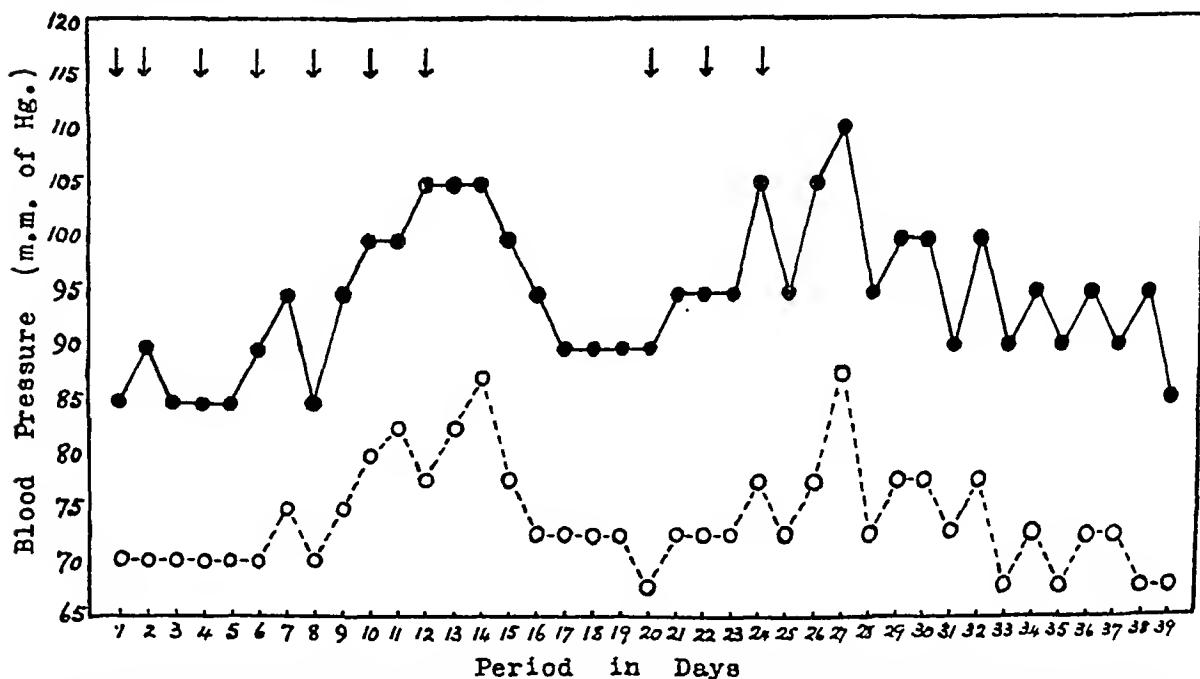


FIG. 2.—Blood pressure chart in Case 12 to show effect of treatment by desoxycorticosterone acetate (D.O.C.A.). Continuous line represents systolic and discontinuous line diastolic pressure. Arrows indicate intramuscular injection of 10 mg. of D.O.C.A.

TABLE I
CARDIOVASCULAR CHANGES IN 13 CASES OF MYOTONIA ATROPHICA

| Case No. | Age | Pulse | | Blood Pressure | First Heart Sound | Voltage of P Wave | Electrocardiographic changes | | | Size of heart at cardioscopy |
|----------|-----|----------|-----------|----------------|-------------------|-------------------|------------------------------|-----------------|--|------------------------------|
| | | Rate | Character | | | | P-R interval (sec.) | Notching of QRS | Other changes | |
| 1 | 23 | 70 | Normal | 120/85 | Normal | Low | 0-20 | Absent | Deep Q in III. | Normal |
| 2 | 29 | 90 | Small | 120/95 | Splitting | Normal | 0-20 | " | Left axis deviation | Appears small |
| 3 | 31 | 70 | Normal | 115/80 | Distant | Low | 0-20 | Present | Variation in electrical potential | Normal |
| 4 | 31 | 100 | Small | 125/100 | Splitting | Normal | 0-21 | " | Left axis deviation. | " |
| 5 | 45 | 70 | " | 135/85 | " | Low | 0-21 | " | electrical potential | " |
| 6 | 36 | 85 | Normal | 140/85 | Normal | " | 0-21 | " | T flat in I. S deep in I and II | Appears small |
| 7 | 42 | 85 | Small | 90/80 | Splitting | Normal | 0-22 | " | T low in I. Left axis deviation. Variation in electrical potential | " |
| 8 | 31 | 75 | " | 110/85 | Normal | " | 0-22 | " | Left axis deviation | " |
| 9 | 31 | 82 | " | 95/80 | Splitting | " | 0-24 | " | " | " |
| 10 | 32 | 85 | " | 120/75 | " | Low | 0-25 | " | " | " |
| 11 | 41 | 50 | Normal | 125/95 | Distant | " | 0-26 | Absent | Atypical bundle branch block | " |
| 12 | 41 | 72 | Small | 85/75 | 4th heart sound | " | 0-30 | Present | Left axis deviation | Moderate enlargement. |
| 13 | 44 | 37 to 48 | Normal | 160/70 | Systolic murmur | " | 0-31 or 2:1 block | " | Left axis deviation Deep Q and S in I | " |

in the myopathic signs although the patient felt much better during the time the blood pressure was raised by the adrenal therapy.

The first heart sound. Impurity of the first heart sound was a common finding and the sound was normal in three cases only. The association of splitting of the sound with a prolonged P-R interval in the cardiogram is shown in Table I. Once a prolonged P-R period gave rise to a triple rhythm from the addition of the fourth heart sound.

Cardiographic changes. A lengthened P-R period was the commonest change in the electrocardiogram. In none of the thirteen cases was the period less than 0.20 sec.; it was 0.24 or greater in five and in two patients it measured 0.30 and 0.31 respectively. In the last case, 2 : 1 heart block was more often present than sinus rhythm (Fig. 3 and 4). In two,

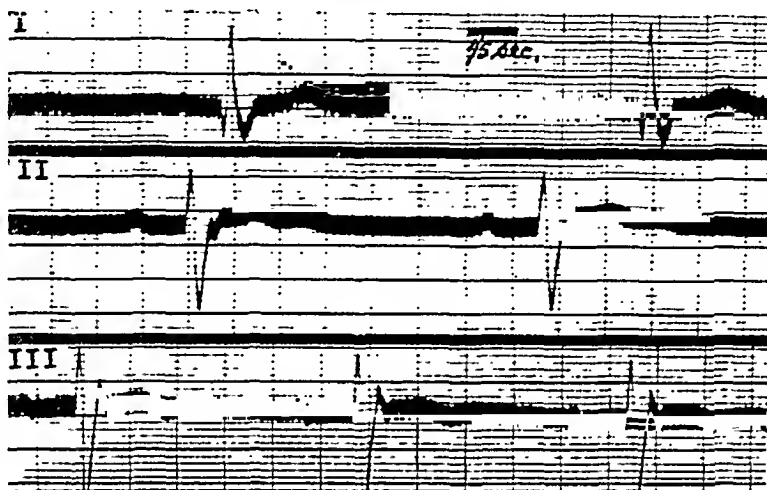


FIG. 3.—Cardiogram in Case 13 during phase of sinus bradycardia. Prolonged P-R period. Small P waves. Slurring of QRS complexes.

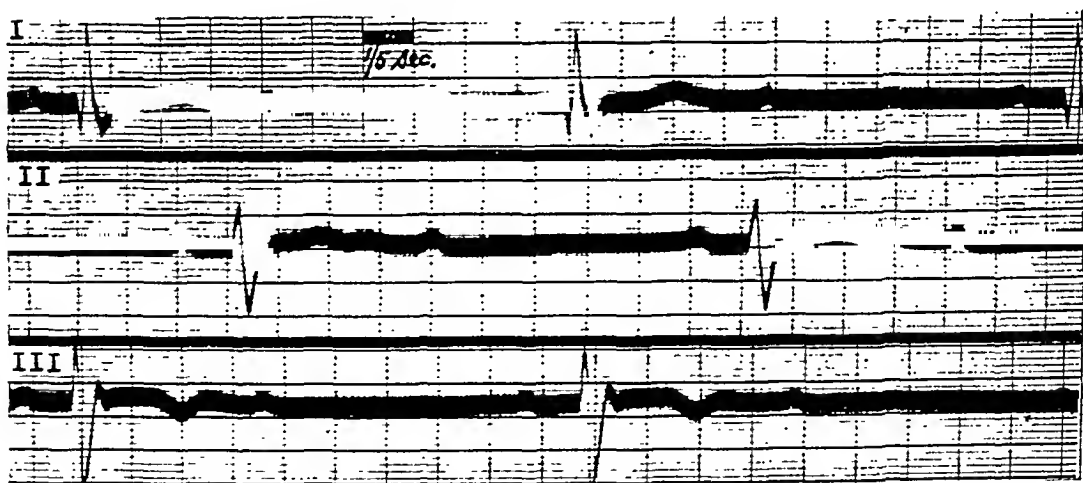


FIG. 4.—Cardiogram in Case 13 during phase of 2 : 1 heart block.

injection of atropine and tachycardia induced by glyceryl trinitrate did not affect the length of the period. Notching of the QRS complex was another common cardiographic abnormality and it was present in nine patients. The Q-S interval, however, was only once greater than 0.10 sec. when it was 0.15 (Fig. 5), giving to the tracing the appearance of left bundle branch block, but unlike such a curve, the T wave was upright in leads I and CR₇. A low voltage of the P wave was the third characteristic change in the electrocardiogram of myotonia atrophica (Fig. 5 and 6); it was present in eight. In the remaining five, the P in lead I was invariably low, but as it was normal in one of the other leads it has not been counted as an

abnormal change. Thus, a well-formed P wave in lead I is an unlikely finding in the cardiogram of a patient with myotonia atrophica. Left axis deviation (Fig. 6) was another common finding (7 out of 13). This was found in the absence of hypertension; it was present when

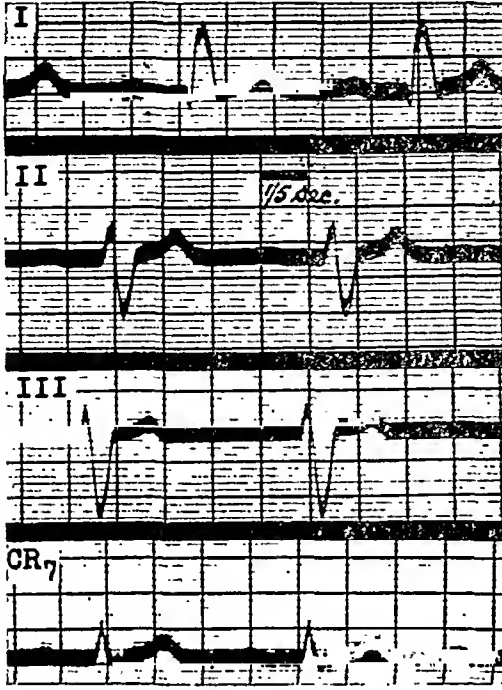


FIG. 5.—Cardiogram in Case 12. Unlike left bundle branch block, T is upright in leads I and CR₇. Prolonged P-R period. Small P waves.

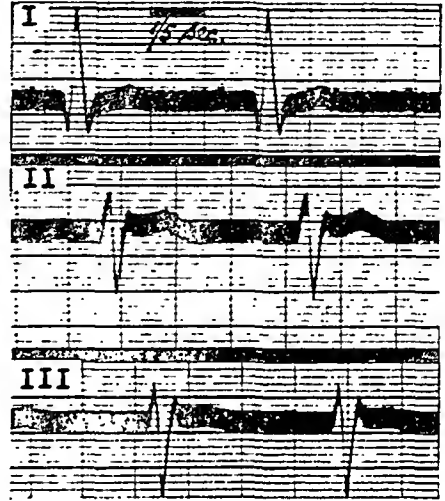


FIG. 6.—Cardiogram in Case 10 showing left axis deviation. Prolonged P-R period. Small P waves.

the blood pressure was low, although it was a feature in three of the four patients in whom the heart was found enlarged at cardioscopy. In two there was no enlargement and the heart appeared to be small in two other cases. Three patients showed a varying electrical potential of the QRS complexes (Fig. 7). It is not suggested that this is a change common to

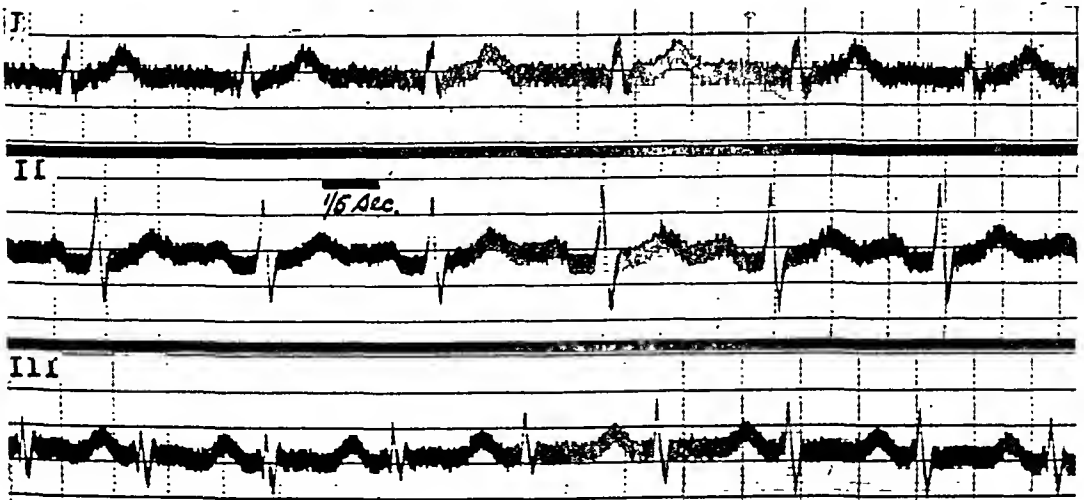


FIG. 7.—Cardiogram in Case 4 showing prolonged P-R period, slurring, and varying electrical potential of QRS complexes.

myotonia for it is not infrequently seen in tracings from healthy subjects, although the incidence of this sign in this series (3 in 13) is somewhat high. Changes in the Q, S, and T waves were inconstant and they have been listed in Table I.

Neither characteristic lens opacity (present in seven), family history of the complaint (common to eight cases), age of the patient, duration of symptoms (over five years in five),



FIG. 8.—Teleradiogram in Case 8. Heart shadow is small in relation to size of chest.

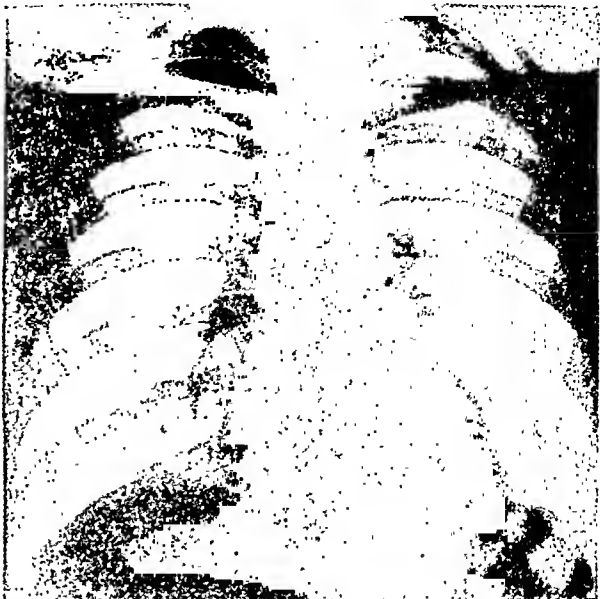


FIG. 9.—Teleradiogram in Case 11 showing slight cardiac enlargement.

nor the severity of the myopathic symptoms, appeared to determine the presence of such cardiographic irregularities.

Size of the heart. No obvious cardiac enlargement could be made out in any of the cases on clinical examination, although the apex beat was a little displaced outwards in two. The actual size of the heart, therefore, was estimated at cardioscopy. In five patients it was judged to be normal, and in four, smaller than was expected when age and stature received

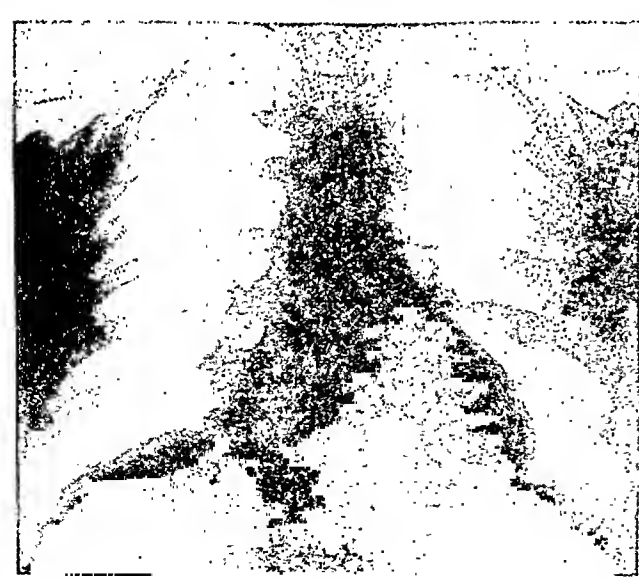


FIG. 10.—Teleradiogram in Case 12 showing moderate cardiac enlargement.



FIG. 11.—Teleradiogram in Case 13 showing moderate cardiac enlargement.

due attention (Fig. 8). In the remaining four the heart was enlarged, slight in two (Fig. 9) and moderate in two (Fig. 10 and 11). The presence of cardiac enlargement was closely

related to, if not dependent on, the length of the P-R period. Thus, when the P-R was 0.24 sec. or less, the heart was not enlarged; in the two cases showing slight enlargement the P-R interval was 0.25 and 0.26, and 0.30 and 0.31 sec. in two others in whom the heart was moderately enlarged. These last two complained of breathlessness on exertion, but there was no evidence of heart failure in either.

SUMMARY AND CONCLUSIONS

Examination of the heart in 13 cases of myotonia atrophica has shown that the presence of cardiovascular signs may help in the earlier diagnosis of the condition.

The pulse is often small and occasionally infrequent. The blood pressure is sometimes very low. The first heart sound in the mitral area commonly shows splitting, and sometimes triple rhythm may appear from addition of the fourth heart sound, this depending on the degree of elongation of the P-R period.

The changes that commonly characterize the electrocardiogram include elongation of the P-R period, low voltage of the P wave, slurring of the QRS complex, and left axis deviation.

The size of the heart varies so that it may be normal or may appear small, but in the presence of considerable lengthening of the P-R period, moderate enlargement takes place.

I wish to thank Dr. John Parkinson, Physician to the Cardiac Department, for his helpful criticism of this paper, and also several colleagues who kindly referred to me cases for this investigation.

REFERENCES

- Adie, W. J. and Greenfield, J. G. (1923). *Brain*, 46, 73.
Carrillo, E. G. (1941). *Rev. Argent. Cardiol.*, 8, 122.
Guillain, G. and Rouquès, L. (1932). *Ann. Med.*, Paris, 31, 158.
Havier, P. and Decourt, J. (1933). *Rev. Neurol.*, 2, 468.
Maas, O. and Zondek, H. (1920). *Z. Neur. Psych.*, 59, 322.
Mondon, H. and Pasquet, D. (1939). *Arch. mal. Cœur.*, 32, 401.
Segura, R. G. and Lanari, A. (1941). *Rev. Argent. Cardiol.*, 7, 363.

SYNCHRONOUS HEART SOUND RECORDING BY APPLICATION OF A SECOND CHANNEL TO THE COSSOR-ROBERTSON CARDIOGRAPH

BY

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By using a microphone to provide the input, the standard Cossor-Robertson cardiograph can be used to record heart sounds instead of the electrocardiogram, but such a record is of little value unless it is recorded synchronously with an electrocardiogram. For this purpose two separate recording channels are necessary. The double-beam cathode ray tube with two amplifying channels has been developed by Donovan (1943). With the addition of stationary spots and a moving-film camera to avoid loss of focus and definition due to curvature of the tube face, this is the method of choice. The possibility of replacing the standard single-beam tube of the Cossor-Robertson cardiograph with a double-beam tube was therefore investigated, but unfortunately it was found that the necessary alterations involved almost complete rebuilding of the instrument.

It is possible, however, to record simultaneously two different wave forms with a single-beam tube by using two valve amplifiers and an automatic switch which connects their outputs alternately to the single deflecting plate of the tube. The effect which this gives is illustrated in Fig. 1. If the switching rate is sufficiently high the gaps in the traces become small com-



FIG. 1.—*Action of Switch.* (A) slow, and (B) more rapid switching rate. As the switching rate is increased the wave form becomes more accurately outlined.

pared with the spot size and each trace appears to be continuous. The passage of the spot from one trace to the other is so rapid that it is not visible. Such switching may be carried out either mechanically or by a thermionic valve device—the electronic switch. Mechanical methods cannot easily provide a switching rate that is sufficiently rapid to record the frequencies of heart sounds and murmurs, but a very efficient type of electronic switch was designed by Clothier (1939). The Clothier circuit is capable of switching between the two

recording channels 2500 times a second, and this very rapid switching rate can be used because the cathode-ray tube provides a recorder free from inertia and with an instantaneous response. The highest frequency that can be adequately recorded depends upon the switching rate (Fig. 1) ; with a rate of 2500 a second it is possible to record satisfactorily the wave form of frequencies up to 200 cycles a second, which is more than adequate for electrocardiography and quite sufficient for cardiophonography. Much higher frequencies can, of course, be recorded, but their wave form will not be completely outlined. With reasonable precautions in design there is no coupling between the two recording channels, so that a potential fed into one amplifier has no influence upon the other trace (Fig. 3).

The Clothier switch can be applied to the Cossor-Robertson cardiograph by connecting the output of its amplifier and the output of an external heart sound amplifier to the switch input. The switch output is connected to the cathode-ray tube. The entire recording system of the cardiograph is used without modification.

Modification of the Cossor-Robertson Cardiograph Recorder Unit

The required alteration is simple, and Messrs. Cossor kindly undertook to carry it out to meet our requirements. It is only necessary to divide the lead from the cardiograph amplifier to the cathode-ray tube, and to bring both ends to terminals on the case ; it is then possible to connect the output of the cardiograph amplifier to the Clothier switch by one terminal (A2),

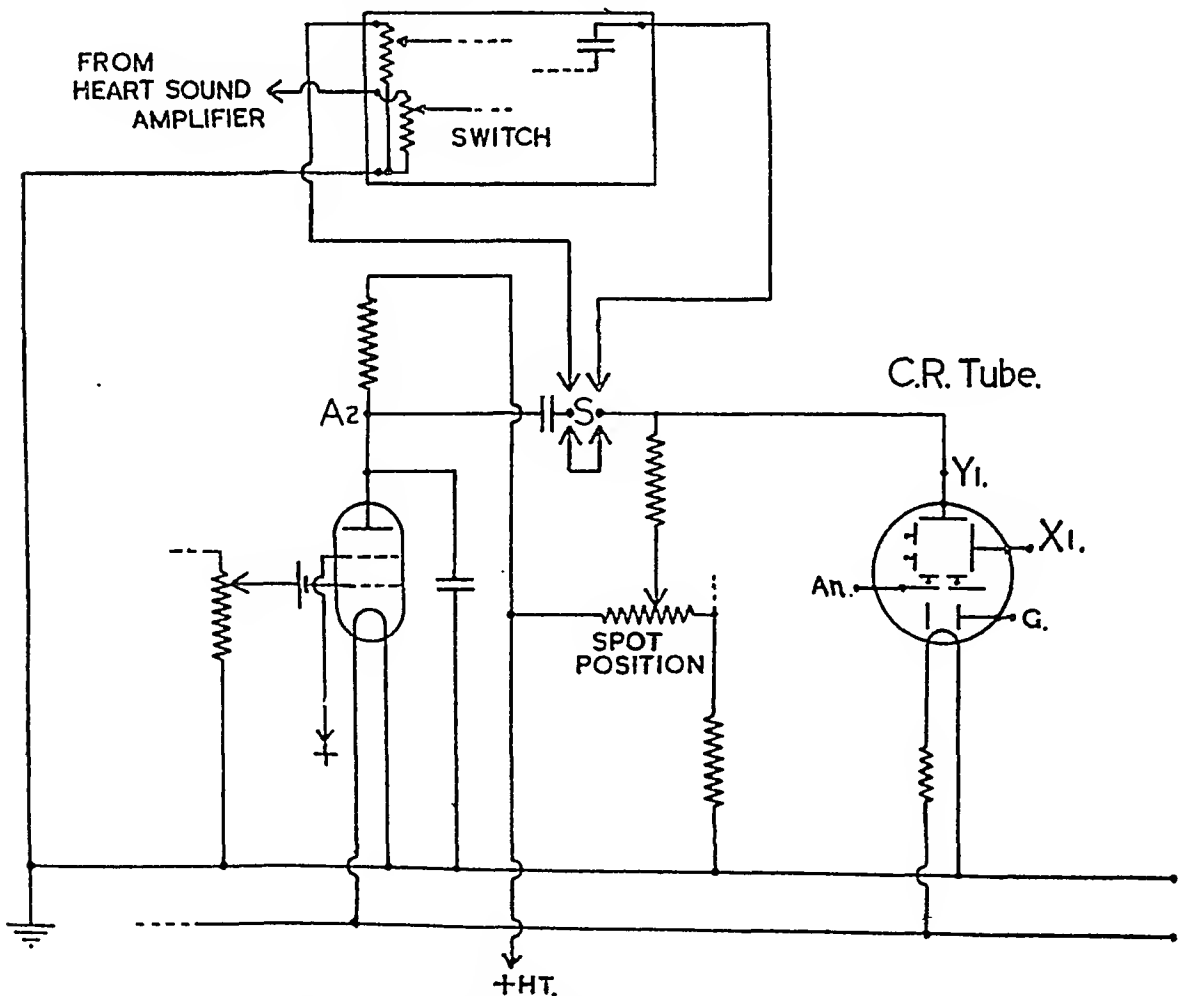


FIG. 2.—Connections of Clothier Switch with Recording Unit. The lead A2 to Y1 in the recorder unit is broken and the two ends brought to the central terminals of a double-pole double-throw switch (S). The switch then permits them to be connected together, restoring the circuit to its original form, or allows Y1 to be connected to the switch output, and A2 to one switch input, as used in the double-channel recorder.

and the switch output can be taken to the cathode-ray tube by the other terminal (Y1). These terminals were fixed on the back of the recorder unit. When Y1 and A2 are connected together the instrument is restored to its original condition and can be used in the ordinary way as a portable cardiograph. It is convenient to incorporate a double-throw double-pole switch so that a single movement converts the simple cardiograph to the double-channel recorder. The connections are shown in Fig. 2. One point of importance must be noted. The introduction of an extra valve in the amplifying system produces a phase shift of 180 degrees in all the potentials amplified. Thus if the deflections of the electrocardiogram are to appear in the same sense as that in which they are normally recorded the patient leads must be reversed.

The Clothier Electronic Switch

It is unnecessary to describe this here for full details have been published by Clothier (1939) and its application to medical purposes has been described elsewhere by one of us (Dawson, 1941).

The Heart Sound Amplifier

A simple resistance-capacity coupled amplifier is suitable, provided it has a frequency response up to 1000 cycles a second, and a gain of 50,000 to 100,000 times. To eliminate slow vibrations, such as movements of the chest and the cardiac impulse, low-frequency filtering is necessary, and this can be introduced by using interstage coupling of suitable value. The degree of attenuation of the lower frequencies depends on the product of the sizes of the grid condenser and the grid leak and, when the values are taken in microfarads and megohms, the product is the time-constant of the coupling. An overall time-constant for the amplifier of 0.1 sec. will attenuate a sine wave of 10 cycles a second by less than 5 per cent. This is the best response likely to be needed in cardiophonography, and increased low-frequency attenuation can be obtained, if required, by switching in grid condensers of smaller values in a single interstage coupling.

When a crystal microphone is used a very simple and satisfactory method of filtering is possible. The impedance of such a microphone is almost purely capacitative and, if the resistance of the load into which the microphone works is reduced, selective attenuation of the low frequencies occurs. The parallel connection of a variable resistance of 1 or 2 megohms allows continuous variation of low-frequency response. The inaudible low components of the heart sounds and of chest pulsations can then be reduced to any desired size.

The connections between recorder unit, Clothier switch, and heart sound amplifier are illustrated in Fig. 2.

Arrangement of the Traces

In order to keep the Cossor-Robertson cardiograph as compact as possible the back of the fluorescent screen is photographed through the side wall of the cathode-ray tube. Light from an image on the upper part of the screen passes very obliquely through the side wall of the tube and this leads to slight blurring of the photographic record owing to the formation of a double image. This is an intrinsic disadvantage of side-tube photography, and can only be overcome by direct photography of the front of the screen. In designing a portable cardiograph the slight blurring of the record when using side-tube photography has been justly regarded as of much less importance than the great increase in bulk which is inevitable when the front of the screen is photographed, and in practice the blurring is largely overcome by using only the lower two-thirds of the screen. In heart sound recording, however, a greater degree of sharpness is advisable and this can be obtained by using only the lower third of the screen from which light passes much less obliquely to the camera. The electrocardio-

gram was, therefore, arranged to occupy the middle third of the screen and the cardiophonogram was placed on the lower third. With side-tube photography it is never possible to obtain records comparable in clarity with those obtained by direct photography of the front of the screen, but it will be seen that this method gives images which are sufficiently clear for most purposes.

The separation of the two traces is controlled by the difference in grid bias of the two switching valves. The two traces tend to set themselves equidistant from a line, the position of which is controlled by the spot position control of the recorder unit. They can thus be moved down to the appropriate position without affecting their separation.

Records

Examples of the records obtained are illustrated in Fig. 3. The input was from a crystal microphone similar to the Cossor cardiophone but with a larger diaphragm opening, which we prefer. It will be noticed that the more rapid deflections of the heart sound records are

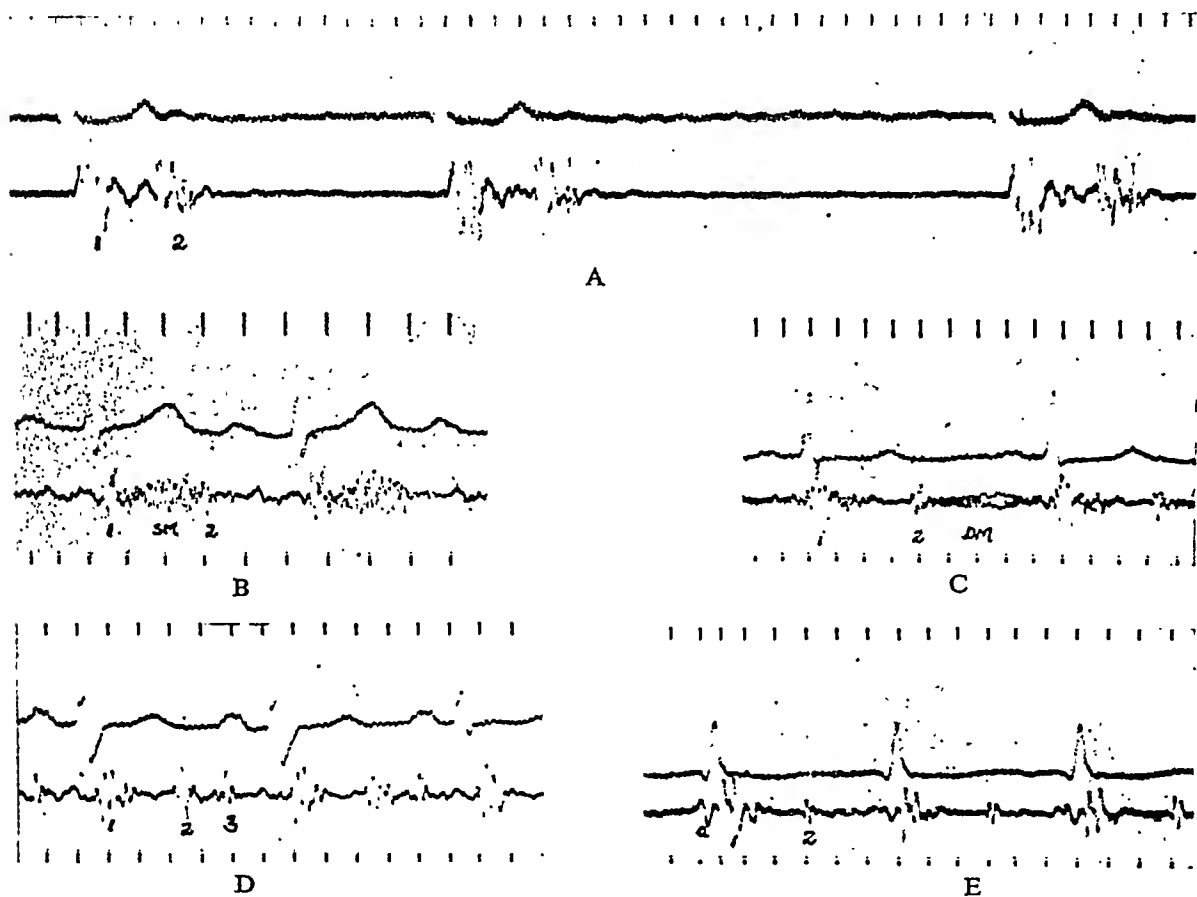


FIG. 3.—Records. (A) Auricular fibrillation. (B) Systolic murmur (S. M.). (C) Diastolic murmur (D. M.). (D) Triple rhythm due to audible third heart sound. (E) Abnormal first heart sound with auricular component (a) which precedes the peak of R. (Time marker : 1/10th sec.).

discontinuous. This is due to the flick of the spot from the cardiophonogram to the electrocardiogram. It will be clear from Fig. 1 that exact vertical alignment (i.e. synchrony) of the traces is automatic and accurate provided that the axis of the tube is set so that the displacement of the spot is truly vertical. It is normally set accurately in this position by the makers, and if far from the correct position it will be found that one trace will fail to record owing to the displacement of the spot outside the camera recording slit.

Summary

A method of synchronous heart sound recording is described in which the standard Cossor-Robertson cardiograph is modified by introducing a second channel using the Clothier electronic switch.

Synchronisation of the tracings is automatic and requires no adjustment.

The alteration to the commercial instrument is simple and does not affect its use as a simple portable cardiograph.

We are indebted to Professor Crighton Bramwell for his interest in this work and to Messrs. A. C. Cossor Ltd., for their co-operation in undertaking the alteration to the Recorder Unit.

The total cost of the conversion, including fitting the terminals to the recorder unit, and the cost of materials for constructing the switch and external amplifier should not, in normal times, exceed £20. In addition a microphone is necessary.

REFERENCES

- Clothier, W. K. (1939), *J. Scientific Instruments*, **16**, 285.
Dawson, G. D. (1942), *Electronic Engineering*, **15**, 722.
Donovan, G. E. (1943), *J. Inst. Elect. Engin.*, **90**, 38.

PAROXYSMAL HEART BLOCK AND VENTRICULAR STANDSTILL

BY

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In auriculo-ventricular block the degree of impairment of conductivity is often found to be inconstant. Even at a time when the rhythm appears clinically to be normal, however, a cardiogram will usually show prolongation of the P-R interval. Only rarely is the conduction normal between the attacks, and the term "paroxysmal heart block" may then appropriately be applied. Reports of 18 such cases have been found, 7 of which had periods of ventricular standstill also; in addition, we found 3 cases of paroxysmal ventricular standstill without heart block (see Starling and Lewis, *infra*).

Hay (1906) described a case in which occasional ventricular beats were dropped, despite regular auricular contractions as shown by the polygraph and unimpaired conduction in the remaining beats; he suggested a depression of ventricular excitability as the cause. His patient was a man of 65 with hypertensive heart disease, and partial heart block had been present in a previous tracing. Gossage (1909) described a similar condition in a woman of 71 with hypertension, and considered it an intermittent form of heart block. In a case recorded by Macintosh and Falconer (1910), a man of 74 had periods of ventricular standstill with Stokes-Adams seizures, during which the auricular rate gradually accelerated, slowing again when the ventricular contractions returned; they were abolished by atropine. Periods of complete A-V block and also of high-grade partial block with a slow irregular ventricular beat were encountered at times. Between attacks, the a-c interval was normal.

Starling (1921) reported the occurrence of periodic ventricular standstill with Stokes-Adams attacks in a man of 51 with a normal-sized heart and a blood pressure of 160/110. Conduction was unimpaired in the intervals. Swallowing used to bring on an attack, but not if atropine had been given during the previous hour. Complete heart block finally supervened. Russell-Wells and Wiltshire (1922) described a male, aged 58, with intermittent complete heart block. The conduction was normal in the intervals. Infective endocarditis was found post-mortem and calcification in the region of the A-V bundle. In the case of Gage and Pardee (1925), a man of 59 with arteriosclerosis, there was intermittent complete block and at other times intermittent ventricular standstill. Conduction was normal in the intervals. Atropine was without effect but adrenaline was followed by ventricular tachycardia, ventricular standstill, and death. Post-mortem, the mitral valve was found to be calcified. Lewis (1925) mentions two cases of intermittent ventricular standstill in patients with normal A-V conduction, in one of which the fibres of the bundle were found to be separated by large venous sinuses. Yater and Williams (1928) described a man of 74 with arteriosclerosis who had periods of normal rhythm alternating with 2 : 1 heart block, complete heart block, and ventricular standstill; post-mortem, there was calcification in the interventricular septum at the junction of its membranous and muscular parts, and invasion of the bundle of His by fibrous tissue. In the case recorded by Wolferth and McMillan (1928), a woman aged 48, periods of partial and complete block were interspersed with normal rhythm during which conduction was unimpaired. Even during phases of partial block, the P-R interval was normal. Atropine

and amyl nitrite increased the auricular rate and the degree of heart block. Arteriosclerosis was present, and the bundle of His was infiltrated by fibrous tissue and round cells.

The case of Carter and McEachern (1931), a man of 63 with hypertensive heart disease, also had a normal conduction time between attacks of complete heart block—attacks that were unaffected by atropine, exercise, or oxygen. Sachs and Traynor's patient (1933), aged 43, had Stokes-Adams attacks during which complete heart block with a very slow idioventricular rhythm was found; during the intervals the P-R interval was normal; atropine had no effect, but the attacks cleared up following recovery from empyema; there was no evidence of disease of heart or arteries. The patient described by Weiss and Ferris (1934) was a man of 64 with moderate arteriosclerosis and a diverticulum in the œsophagus. Fainting attacks occurred when he swallowed and were found to be due to complete heart block. When a balloon was passed into it and distended, prolongation of the P-R interval was produced, and then complete A-V block, which could be prevented by atropine, or by the injection of procaine into the vagus in the neck so that it was evidently a vagal reflex. Comeau (1937) reported a case of paroxysmal heart block in a woman of 76; the P-R interval was normal between the attacks and these were not abolished by atropine: permanent heart block eventually supervened. A similar case in a man, aged 57, went on to permanent block after two-and-a-half months. Gilchrist (1937) reported two cases of intermittent heart block, both in elderly persons; normal rhythm without delayed conduction was usually followed by ventricular standstill and this by a period of complete A-V block: both patients were benefited by ephedrine. Parkinson, Papp, and Evans (1941) reviewing the subject of Stokes-Adams attacks record the case of a male, aged 43, in whom periods of ventricular standstill started with a delayed auricular beat not followed by a ventricular complex and ended with an ectopic beat 0.1 sec. after P, after which sinus rhythm was resumed without impairment of conduction. Paroxysms lasted 5-20 seconds. There were also occasional periods of complete block. He showed no other evidence of cardiac abnormality and attacks ceased after a month. Of 38 cases of partial heart block with dropped beats recorded by Campbell (1943), 3 had paroxysmal block. One, a woman aged 66 with hypertensive heart disease, had phases of sinus rhythm, dropped beats and complete heart block; the P-R interval was 0.21 sec., which is within normal limits according to Chamberlain and Hay (1939). One in his series had at one time a 2 : 1 heart block with a P-R interval of 0.19 sec. or less, a man of 55 with congestive failure; the third, a woman aged 25, was rather different as the heart block was temporary and due to active rheumatic carditis. [Three others have been added in the paper that follows this—Cases 101, 106, and 115 (Campbell, 1944).]

OBSERVATIONS

Our own case, a retired gardener, aged 71, stated that he had been in good health till four years previously when his ribs were injured in an accident. He noticed some dyspnoea on exertion after this but returned to work. Six months later, however, the dyspnoea was so bad that he had to give up his work and had not returned since. Three years ago he had attacks of nausea, relieved by food; and a few weeks later, attacks that started with a tingling in the legs, passing up to the head, and then severe pain in the head; he would fall forward, dazed but not unconscious. These attacks recurred frequently and two years ago during a severe one he lost his power of speech and had convulsive movements of the limbs. This was the first occasion of his admission to hospital. He was found to have a pulse rate of 35-40 with occasional coupled beats. After an attack of unconsciousness, stated to have lasted 4-5 minutes, his pulse rate rose to 70 per minute. No cardiogram was taken at that time. After discharge from hospital, he continued to have attacks several times a day with occasional remissions lasting a few days. Latterly the attacks have started with pain in the left side followed by palpitation, slow at first but accelerating (probably the auricular contractions). He had to sit down and usually became unconscious for a few seconds; sometimes uncon-

sciousness was more rapid and he fell to the ground. He was readmitted in September, 1942. He was found to be of plethoric type. The pulse was slow and for the most part irregular, varying from 24–56 per minute. The auricular wave could be seen in the neck beating regularly at 80 a minute so that the ventricles on these occasions appeared to be responding to every third beat. Sometimes every beat of the auricles was followed by a ventricular contraction for a minute or so and this would alternate with periods of ventricular asystole during as much as nine consecutive beats of the auricle. During these periods of ventricular asystole, the patient became pale, anxious, and restless, and the auricular waves in the neck gradually became more rapid and forcible. When the ventricles again started to beat, the face immediately flushed, the patient's anxiety and restlessness passed off, and the auricles resumed their previous rate.

The maximum blood pressure was 180/80 mm. The arteries did not appear thickened. There was a systolic murmur, maximal at the apex. No abnormal signs were found in the remainder of the physical examination, apart from absence of the knee jerks and a tremor of senile type in the hands. The urine showed no abnormality. The blood W.R. was negative.

Fluoroscopy showed the heart to be of normal shape and size. On the first occasion the ventricles were responding to every auricular beat, but on a second occasion periods of ventricular asystole were observed and the increasing speed and force of the auricular contractions at these times was confirmed.

Fig. 1, taken on admission, showed an unusual rhythm. There was for the most part, complete dissociation between auricles and ventricles, the auricles beating at 70 a minute, the



FIG. 1.—On admission. There is complete heart block except when a P wave follows immediately on a ventricular complex when the impulse is conducted normally.

ventricles at 23. At irregular intervals the slow idioventricular rhythm was interrupted by an added ventricular beat which always followed a P wave at an interval of 0.2 sec. These added beats occurred only when the P wave happened to come soon after one of the ventricular complexes. The picture therefore was one of complete heart block, with the ventricles responding to an occasional auricular contraction with a normal conduction time. The ventricular complexes were normal apart from slurring of S I and a biphasic T IV.

After his admission, when no drugs were given, the pulse continued to vary as already described and Stokes-Adams attacks were numerous. Ephedrine was then administered at

4-hourly intervals in increasing doses from 0.5–2 grains. No alteration occurred in the pulse and attacks continued to be numerous. The treatment had to be abandoned in a few days, as it was found to produce retention of urine (the prostate was much enlarged).

Digitalis was then given, the initial dose being half a grain of the powdered leaf, t.i.d., rising to 2.5 grains, t.i.d. Stokes-Adams attacks became less numerous and the pulse, though varying between 20 and 56 a minute, showed less irregularity. Fig. 2 showed that the auricular rate was slower (50) and that, at the time of the tracing, the ventricles were responding to every second beat, the P–R interval being of normal duration (0.18 sec.). Numerous ventricular extrasystoles were present. The P wave was low in all leads but best seen in the right pectoral lead (right arm lead to right arm, chest lead applied at the fourth intercostal space just to the right of the sternum). In the limb leads the QRS complexes had become widened,

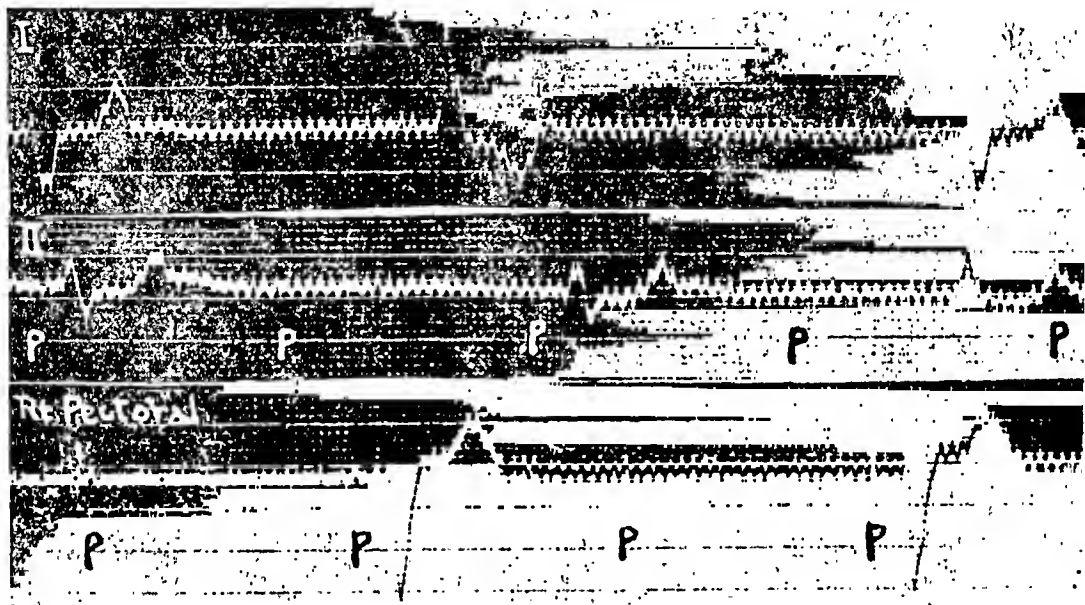


FIG. 2.—The patient is receiving 7.5 grains of digitalis powdered leaf daily. The auricular rate has become slower and the ventricles are responding to alternate auricular beats.

R I and R II diminished, and S I increased. On another occasion, when the patient was still having digitalis, (Fig. 3), he showed a normal sinus rhythm punctuated by periods of ventricular asystole, varying in duration from 6–11 seconds: the auricular rate was 45 and the P–R interval 0.2 sec. During the phases of ventricular asystole the auricular rate steadily increased up to about 60 a minute and then when normal rhythm had returned slowed down to 45 again; the first ventricular systole was not accurately related to the preceding P wave, the P–R interval being 0.3–0.48 sec. and was therefore presumably an idioventricular beat. It was sometimes followed by a missed beat or a ventricular extrasystole before a normal sequence was re-established. As this type of rhythm had been noted before giving digitalis, it was evidently not due to the drug. The inversion of QRST in this and subsequent records could not be accounted for, except possibly by alteration of posture.

Belladonna, 20 minims, t.i.d., resulted in more frequent Stokes-Adams attacks. The auricular rate rose to 90 and, at the time of the cardiogram, the ventricles were responding to alternate stimuli. Such phases were unfortunately very transient and infrequent.

Barium chloride, 1 grain 4-hourly, was without effect. Adrenaline hypodermically merely produced retention of urine.

At this stage it was felt that, as belladonna and ephedrine had not affected the dysrhythmia, it was unlikely to be due to a vagal reflex as in the case reported by Weiss and Ferris (1934). A spasm or partial occlusion of one of the small arteries supplying the bundle of His seemed a

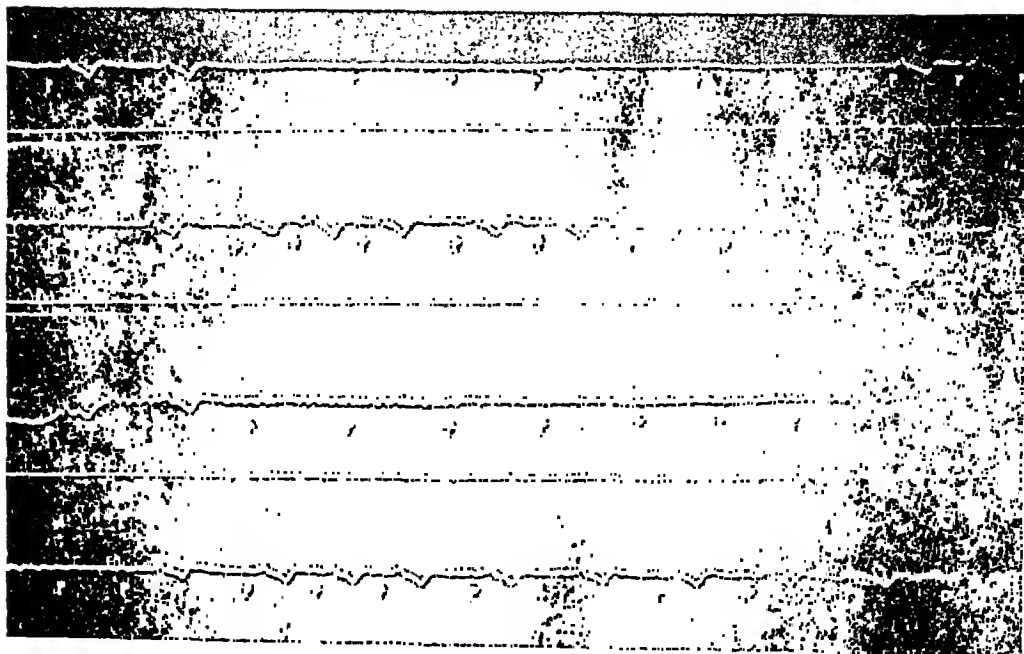


FIG. 3.—Paroxysmal ventricular standstill alternating with normal rhythm (right pectoral lead).

possible cause, so amyl nitrite was next administered. Thirty seconds after inhaling a 2-minim ampoule, the pulse, which before had been beating irregularly at 28, rose to a rate of 70 a minute and became regular, remaining so for the next half hour. In Fig. 4, taken just after the inhalation of amyl nitrite, auricles and ventricles are both beating at 70 a minute, the P-R interval being 0.16–0.2 sec. Just before this tracing, intermittent ventricular standstill had



FIG. 4.—Immediately after the inhalation of amyl nitrite. A normal sinus rhythm, rate 70 a minute. The inverted T wave was of similar magnitude before the inhalation (see Fig. 3) (right pectoral lead).

been present as in Fig. 3. Unfortunately glyceryl trinitrini and sodium nitrite were without effect, but by inhalations of amyl nitrite whenever minor attacks began to appear, it was found possible to keep the patient fairly well stabilized. To facilitate this and to avoid the expense of numerous glass capsules, a small wide-mouthed, glass-stoppered bottle was filled loosely with cotton wool and this was soaked with amyl nitrite. The patient kept this by him and inhaled from it whenever the periods of ventricular asystole became troublesome. He soon learned how much to inhale in order to abort the attacks, but no harm resulted if he continued to inhale till the pulse became regular and rapid.

To test further the theory of coronary spasm, the effect of other substances acting on the coronary arteries was studied. Adrenaline dilates the coronary arteries, but also by raising the blood pressure stimulates the vagi through the carotid sinus and aortic nerves (Wright, 1930), so producing an opposing constrictor effect. If the vagus is blocked by atropine, this constrictor effect is avoided and dilatation occurs. Atropine and adrenaline in doses of 0.5 mg. of each were accordingly injected subcutaneously. The pulse rate rose from 30 to 66 in 25

minutes and eventually to 75 where it remained for over two hours. Fig. 5 showed the auricles and ventricles beating normally at 75 a minute, with a P-R interval of 0.2 sec. Ventri-



FIG. 5.—After administration of adrenaline and atropine. A normal sinus rhythm is present, rate 75 a minute (right pectoral lead).

cular extrasystoles were numerous at first but these had disappeared after one-and-a-half hours, leaving a pure sinus rhythm.

Both lack of oxygen and excess of carbon dioxide cause dilatation of the coronary arteries. The former, however, does not increase the oxygen consumption of the heart muscle, as the increased coronary flow merely keeps pace with the diminished oxygen saturation (Hilton and Eichholtz, 1925). Thus only excess of carbon dioxide without lack of oxygen will increase the oxygen available to the myocardium. Lack of oxygen was produced in this case by breathing nitrogen through a B.L.B. mask till cyanosis appeared. In Fig. 6, obtained at this



FIG. 6.—Record taken during a period of induced lack of oxygen. There is complete A-V block and ventricular contractions are arising from a number of different foci (right pectoral lead).

time, there is complete A-V block with ventricular complexes arising from a number of different foci.

Carbon dioxide was administered at a concentration of 5 per cent in oxygen. It resulted in the ventricles responding to alternate beats of the auricle, a ventricular extrasystole following each normal beat; the P-R interval was 0.2 sec.

Freedberg, Riseman, and Spiegl (1941) have shown that quinidine reduces the tendency to effort pain in angina pectoris, and prevents the cardiographic changes usually associated with the attack. When this drug was given to our patient in doses of 3 grains 3-hourly, the pulse became, for the most part regular at a rate of 30-32 a minute with occasional more rapid periods (62-70). The cardiogram showed complete heart block, the auricles beating at 75, the ventricles at 33; numerous extrasystoles were present at the time of the record. No Stokes-Adams attacks occurred during the first week of this treatment but during the second week occasional severe attacks occurred. During one of these, the ventricular contractions failed to return and the patient died.

Post-mortem examination showed no gross abnormality in the heart. Small atheromatous plaques were scattered throughout the coronary arteries but these were not sufficient to

obstruct the lumen at any point. No pathological change was evident in the A-V bundle or in any other part of the myocardium.

DISCUSSION

Of the 22 cases reviewed in this paper, 8 had intermittent heart block, 5 had intermittent ventricular standstill, and 9 exhibited at different times both phenomena. In all these cases conduction through the bundle of His was normal between the attacks, even when, as in 4 of the cases of ventricular standstill, only a single beat was missed at a time. These latter cases could be differentiated from partial heart block only by the normal P-R interval in intervening beats. In 4 of the cases, however, transient periods of partial block were noted in addition to periods of complete heart block and ventricular standstill.

The effect of drugs was not uniform. Atropine abolished the attacks temporarily in 4; ephedrine was effective in 2, adrenaline in 1 case. In 1, injection of procaine into the vagus abolished the attacks temporarily. The condition was aggravated by both atropine and amyl nitrite in 1, the only other case in which amyl nitrite appears to have been tried.

Of the patients 13 were males and 5 females, and in 4 the sex was not given. The ages ranged from 25 to 76, the average being 59. Calcification or fibrosis was found in the bundle of His in 4, and large venous sinuses in 1 case. Hypertension or arteriosclerosis was present in 10; in 1, a diverticulum of the œsophagus was shown to be the cause.

The frequency with which intermittent heart block and intermittent ventricular standstill, though both very rare, are associated in the same patient indicates a common cause. An intermittent depression of excitability of the ventricular muscle, as suggested by Hay, explains the periods of ventricular asystole but not the periods of partial or complete block. Moreover, digitalis, which increases the excitability of the heart muscle, does not abolish the periods of ventricular asystole, but seems rather to lengthen them; and quinidine, which depresses the excitability of the heart muscle, does not render them more frequent though possibly more prolonged.

Spasm or partial occlusion of an artery supplying the conducting bundle would account for both the intermittent block and the ventricular standstill, assuming that the bundle fibres were capable of immediate recovery following the short periods of anoxæmia so produced. In favour of this hypothesis, hypertension or arteriosclerosis was observed in half the cases, and all except one were in the latter half of life. Further, in the authors' case, amyl nitrite abolished the attacks in 30 seconds (amyl nitrite takes 30-60 seconds to produce its full dilator effect on the arterioles); atropine and adrenaline together were effective, but not separately; inhalation of carbon dioxide reduced the degree of heart block; and during "complete" heart block, an auricular wave falling immediately after ventricular systole would be conducted through the A-V bundle and give rise to an added ventricular beat. It is in early diastole that the coronary flow reaches its maximum according to Anrep (1926) (for record see Fig. 1). Finally, prolonged ventricular asystole was always followed, after one or two idioventricular contractions, by a phase of normal sinus rhythm. This may be explained as follows. Ischæmia of the A-V bundle due to arterial spasm or partial occlusion blocks the passage of the contraction wave, and ventricular standstill results. This gives rise to a rapidly increasing cerebral and coronary anoxæmia and an accumulation of carbon dioxide in the blood. These three factors all have the effect of dilating the coronary arteries (Hilton and Eichholtz, 1925; Anrep and Segall, 1926), but the coronary anoxæmia still impairs the function of the bundle, and impulses continue to be blocked. Eventually idioventricular contractions appear as in commencing complete heart block. This causes a surge of oxygenated blood through the now widely dilated coronary arteries, thus restoring the function of the bundle. Cerebral anoxæmia and the excess of carbon dioxide are relieved and the tone of the coronary arteries returns so repeating the cycle.

It is unlikely that ischæmia of the A-V bundle is the mechanism responsible for all cases of

paroxysmal heart block and ventricular standstill. A simple inhibitory action of the vagus on the A-V bundle may have been the cause in those cases relieved by atropine, especially the case of Weiss and Ferris in which distension of the œsophageal diverticulum produced an attack, but, as the vagus contains vasoconstrictor fibres to the coronary arteries, ischæmia may have played a part here also.

SUMMARY

A case is described showing periods of intermittent heart block and occasionally a phasic ventricular standstill. Conduction was normal in the intervening stages.

Eighteen reported cases of this type are reviewed.

It is suggested that arterial spasm or partial arterial occlusion is the main factor in the majority of these cases.

It was found possible to control the attacks by inhalations of amyl nitrite.

We wish to express our thanks to Dr. R. A. Hill, Medical Superintendent of Haymeads Emergency Hospital for facilities granted.

REFERENCES

- Anrep, G. V. (1926). *Physiol. Rev.*, 6, 596.
 —, and Segall, H. N. (1926). *Heart*, 13, 239.
 Campbell, M. (1943). *Brit. Heart J.*, 5, 55.
 — (1944). *Ibid.*, 6, 69.
 Carter, E. P., and McEarchern, D. (1931). *Bull. John Hopkins Hosp.*, 49, 337.
 Chamberlain, E. N., and Hay, J. D. (1939). *Brit. Heart J.*, 1, 105.
 Comeau, W. J. (1937). *Amer. J. med. Sci.*, 104, 43.
 Gage, L. J., and Pardee, H. E. B. (1925), *ibid.*, 169, 656.
 Gilchrist, A. R. (1937). *Brit. med. J.*, 1, 203.
 Gossage, A. M. (1909). *Heart*, 1, 283.
 Hay, J. (1906). *Lancet*, 1, 139.
 Hilton, R., and Eichholtz, F. (1925). *J. Physiol.*, 59, 413.
 Lewis, T. (1925). *The Mechanism and Graphic Registration of the Heart beat*, 3rd. ed., London, 421.
 McIntosh, A. W., and Falconer, A. W. (1910). *Heart*, 2, 222.
 Parkinson, J., Papp, C., and Evans, W. (1941). *Brit. Heart J.*, 3, 171.
 Russell-Wells, S., and Wiltshire, H. W. (1922). *Lancet*, 1, 984.
 Sachs, A., and Traynor, R. L. (1933). *Amer. Heart J.*, 9, 267.
 Starling, H. J. (1921). *Heart*, 8, 31.
 Weiss, S., and Ferris, E. B. (1934). *Arch. intern. Med.*, 54, 931.
 Wolferth, C. C., and McMillan, T. M. (1928-9). *Amer. Heart J.*, 4, 521.
 Wright, S. (1930). *J. Physiol.*, quoted by Wright (1940), *Applied Physiology*, 7th. ed., 193, London.
 Yater, W. M., and Willius, F. A. (1928-9). *Amer. Heart J.*, 4, 280.

HEART BLOCK WITH ANEURYSM OF THE AORTIC SINUS

BY

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Disturbances of conduction in the heart may be purely functional, when for example demands are made on the conduction path very early in diastole as seen in blocked and aberrantly conducted auricular extrasystoles (Scherf and Boyd, 1940), or when too many stimuli are presented for conduction within a short time as with the incomplete A-V block that always exists in auricular fibrillation. Conduction disturbances may also be due to vagal inhibition. They may occur transiently after pneumonia and influenza, and are well known in diphtheria; recently Neubauer (1942) found many examples of partial and complete block in 100 cases of diphtheria. Over-digitalization may through poisoning of the A-V node lead to prolongation of conduction time, partial, or complete block. A permanent block can be established through coronary sclerosis, coronary thrombosis, rheumatic heart disease, syphilitic gumma, and more rarely through diphtheria, tuberculosis, and carcinoma affecting the A-V node or bundle directly. Congenital complete heart block is also known, and a few cases were found by Yater (1929), Aitken (1932), Campbell and Suzman (1934), and Currie (1940). The exceptional event of heart block as a result of direct trauma to the chest wall is described by Coffen (1930), Walker (1933), and White (1937).

The following is the report of a case in which complete heart block was associated with an intracardiac aneurysm and aortic stenosis.

A farm labourer, 49 years of age, was admitted to the General Hospital, Northampton, on September 16, 1942. He had been off work since the beginning of July 1942, because of tiredness, dizziness, loss of weight, pains "all over the body," pain and frequency of micturition, and on one or two occasions attacks of hæmaturia. Mainly because of the urinary symptoms he was sent to hospital. Twenty years ago he had diphtheria, but had always enjoyed fairly good health otherwise, except for a regular winter cough. His father and one sister had died of tuberculosis. He was married and had three children aged 1, 7, and 10 years, who were all well; there had been one miscarriage and one stillbirth.

On admission he complained of the above-mentioned symptoms, but his appetite was good and there was no cough, breathlessness, headache, vomiting, abdominal pain, or swelling of the ankles. He was pale and rather thin, but well built. Temp. 99, resp. rate 20, pulse rate 36. There was marked clubbing of the fingers and toes. The cardiac impulse was felt in the fifth intercostal space, one inch outside the mid-clavicular line, and was of a heaving character. A thrill could be felt in the aortic area where there was a loud and rough systolic murmur, which was propagated to the neck and towards the right axilla; a systolic murmur was also audible in the mitral region traceable towards the left axillary line. The blood pressure was 100/75 on the right side, and 120/60 on the left. The pulse was markedly anacrotic and of fair volume in the right arm, while in the left it was of a better volume but not anacrotic. The neck veins were not engorged and showed no abnormal pulsation. The liver was not enlarged; the spleen and kidneys were not palpable. Nothing abnormal could be found in the lungs. There was some slight tenderness in the suprapubic region. The urinary symptoms were proved to be due to subacute cystitis, which cleared up within a fortnight. A radiograph of the chest showed the heart enlarged to the left with rounding of the apex, no broadening of the aortic shadow, and clear lungfields. Fig. 1 taken on September 22 shows a lævocardiogram with regular auricular and regular ventricular activity but continuous variation in the length of the P-R interval. The

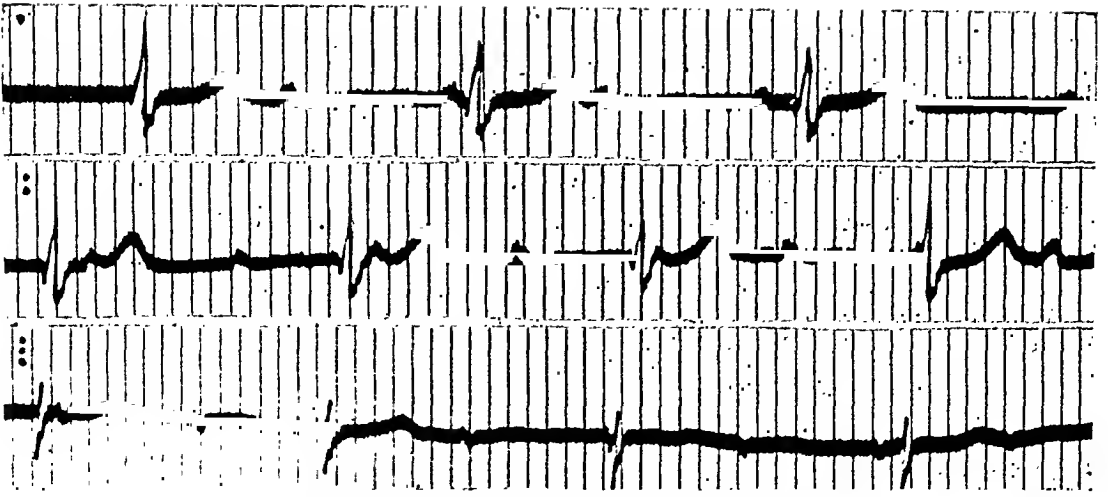


FIG. 1.—Complete heart block and left axis deviation. Auricular rate, 86; ventricular, 40 a minute.



FIG. 2. View of the heart opened from the front. A rod is placed into the entrance to the aneurysm behind the right posterior aortic valve. The whole aortic ring is severely calcified; the aorta itself and the mitral valve are unaffected.

auricles contract at a rate of 86, the ventricles at a rate of 40 beats a minute. The width and shape of the ventricular complexes (broadened to 0.12 sec. and slightly slurred) cannot be evaluated as indicating a myocardial lesion; the excitation spreads abnormally within the ventricles due to the fact that deep, abnormally located centres have assumed control. There is no displacement of the S-T segment, and the T waves are upright in all leads. The Wasserman reaction was negative.

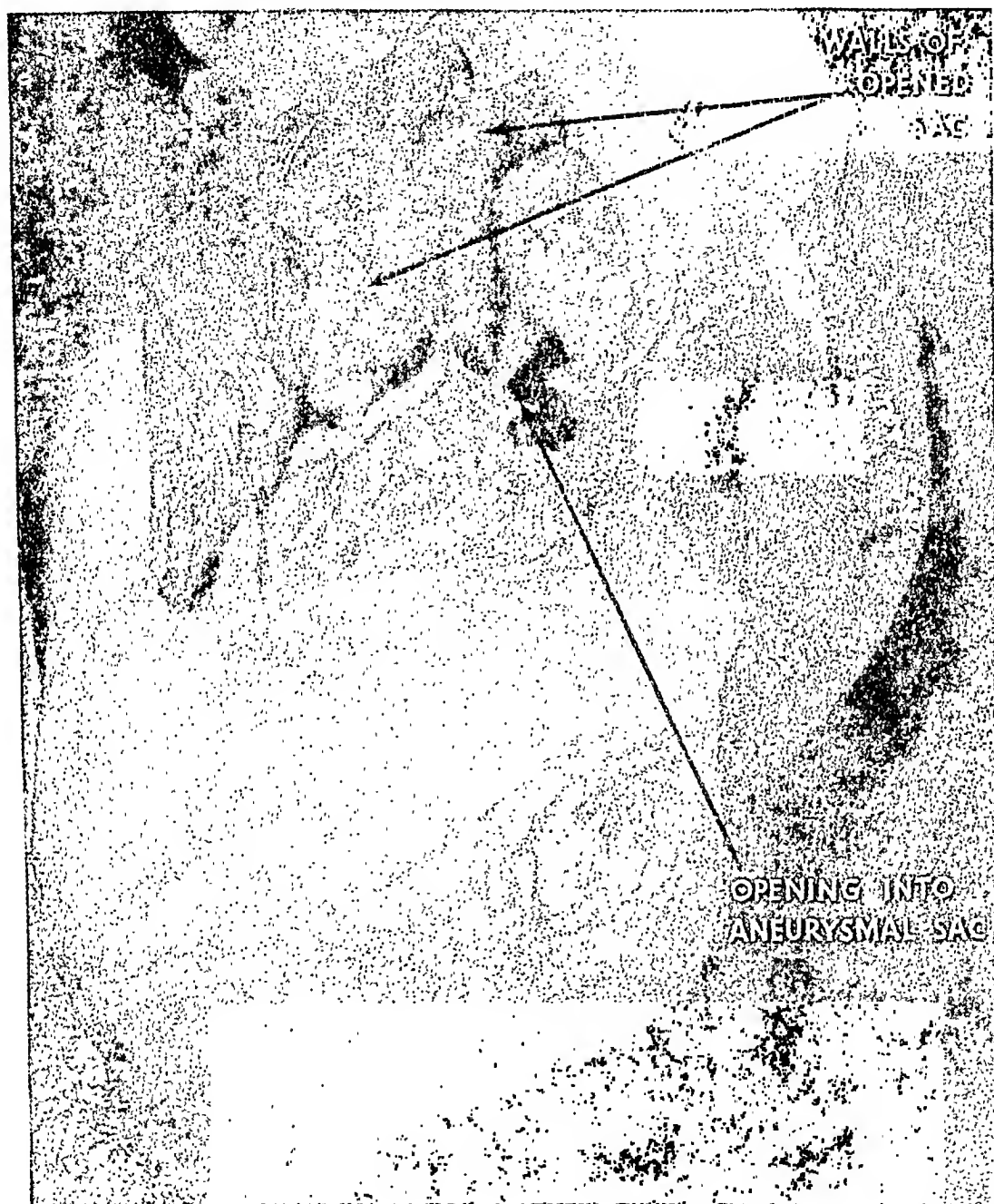


FIG. 3.—View of the right auricle, and of the aneurysm, the walls of which have been cut open and the two halves folded back. The rod appears in the lower part of the aneurysm and shows the communication with the aorta. The two upper arrows point to the two halves of the aneurysm.

Aortic stenosis and complete heart block was diagnosed, and a tentative diagnosis of an aortic aneurysm was considered. The patient was about to be discharged from the hospital on October 1, 1942, when it was noted on the evening of the day before that his temperature was 99.2; the next day it had risen to 100 and remained there until October 5; no cause could be found for the temperature, and the patient felt well and had no complaints. On the morning of October 6 he woke up at 5.30 a.m. feeling clammy and faint, and found it difficult to get

his breath. He was examined ten minutes later. The pulse was of a good volume and regular, but the rate had dropped to 22. He was not cyanosed, but was grey in colour, cold and clammy and very dyspnoëic. He improved on coramine and brandy, but three-quarters of an hour later he died suddenly, presumably due to more profound slowing of the ventricular rate with ultimate standstill.

At necropsy the brain was not examined. The lungs were voluminous, but not congested; they appeared to be normal, apart from a healed apical lesion on the left side. The pleural cavities were normal. The pericardium contained some clear fluid. The heart was hypertrophied, mainly in the left ventricle, and the right auricle was dilated. The tricuspid, mitral, and pulmonary valves were normal. A saccular aneurysm of about 1 1/2 inch diameter was found projecting into the right auricle, lying on the lower part of the interauricular septum and communicating with the aorta through a 1/4 inch diameter passage immediately above the right posterior aortic valve. There was severe calcification of the aortic valve ring which was continuous with the wall of the aneurysmal sac (Fig. 2 and 3). The aneurysm was not ruptured. The aorta and blood vessels, including the coronary arteries, showed no atheroma. The liver and spleen were slightly enlarged and showed early venous congestion. The gastrointestinal tract and the pancreas were normal.

DISCUSSION

The ascending part of the aorta is normally a little enlarged just above its origin; this enlargement consists of three small pouches, known as the sinuses of Valsalva, opposite to which are attached the three semilunar valves. Aneurysm may develop here and involve one, two, or all three of these sinuses of the aorta. They rarely attain a size to produce physical signs, and before symptoms appear can lead to sudden death, which may be of medico-legal interest. Death occurs through perforation, either into the pericardium or more rarely into the superior vena cava, pulmonary artery, or right or left auricle. Syphilitic aortitis is usually the cause but a few cases were found with ordinary atheromatous changes. The aortic valves are as a rule affected. Whilst I am not acquainted with a publication of a case similar to the above described, I found a reference to the aneurysm of the sinus of the aorta by Matthes (1928) who states that it is a very rare occurrence, that it affects usually the right sinus, and that it may develop into the right ventricle, more rarely into the right auricle, or outwards and upwards. He further mentions that these aneurysm can be diagnosed only if they burst, and thus lead to a conspicuous alteration of the whole clinical picture, e.g. the sudden occurrence of a very loud murmur which extends over both heart phases, and was not present previously. In any case one can only make the diagnosis if one knows that the aortic valves are diseased.

Reference should also be made to the case of Micks (1940) who found aneurysms of all three sinuses of Valsalva; the patient developed complete heart block before his death.

In trying to find the cause of the heart block it appears that four possibilities have to be considered.

1. The absence of any fainting attacks may suggest that the block was congenital. The patient was carefully interrogated as to any previous loss of consciousness, etc., but denied firmly any such occurrence. On the other hand, he volunteered the information that his fingers were clubbed as long as he could remember. However, the postulates of Yater (1929), concerning congenital heart block, are not completely fulfilled, and in view of the other findings this possibility is not very likely.

2. He had diphtheria twenty years ago. There is as yet no conclusive evidence as to the after-effects of diphtheria on the heart. In 100 cases which had suffered from diphtheria 5 to 10 years previously Jones and White (1927) did not find any signs of heart disease. Hoskins (1926), on the other hand, found persistent cardiographic changes quite common after diph-

theria, and Butler and Levine (1929) found a history of diphtheria in 10 out of 20 patients with heart block of obscure origin, and believe that diphtheria is of ætiological significance in many such cases.

3. The aortic valve ring was severely calcified, causing aortic stenosis. Auricular-ventricular or bundle branch block is an occasional complication of aortic stenosis; this may be due to extension of the calcifying process from the aortic ring into the interventricular septum with implication of the bundle of His. Unfortunately a histological examination of the bundle was not made in this case.

4. The aneurysmal sac was situated close to the auricular part of the Aschoff-Tawara node, and it is most likely that the pressure of the aneurysm on the node caused the block. On this assumption the post-mortem report as to the cause of death was as follows: Aneurysmal sac of aorta, pressing on bundle of His, secondary to ulcerative changes in the aortic valve ring.

SUMMARY

A case is reported with an aneurysm of a sinus of Valsalva and complete heart block. The possible causes of the block are discussed, and the conclusion is drawn that the block was due to pressure of the aneurysm on the conducting path.

My thanks are due to Dr. W. M. Robson for permission to report the case, and to Dr. Margaret Masson for the photographs (Fig. 2 and 3) and most helpful co-operation.

REFERENCES

- Aitken, Janet (1932). *Lancet*, 2, 1375.
Butler and Levine, S. A. (1929). *Amer. Heart J.*, 5, 592.
Campbell, M. and Suzman, S. (1934). *Ibid.*, 9, 304.
Coffen, T. H. (1930). *Ibid.*, 5, 667.
Currie, G. M. (1940). *Brit. med. J.*, 1, 769.
Hoskin, J. (1926). *Lancet*, 1, 1141.
Jones, T. D. and White, P. D. (1927). *Amer. Heart J.*, 3, 190.
Matthes, M. (1928). *Lehrbuch der Differentialdiagnose Innerer Krankheiten*, Berlin.
Micks, R. H. (1940). *Brit. Heart J.*, 2, 63.
Neubauer, C. (1942). *Brit. med. J.*, 2, 91.
Scherf, D. and Boyd, L. J. *Clinical Electrocardiography*, London.
Walker, G. F. (1933). *The Injured Workman*, Bristol.
White, P. D. (1937). *Heart Disease*, New York.
Yater, W. M. (1929). *Amer. J. Dis. Child.*, 38, 112.

STOKES-ADAMS ATTACKS IN A CHILD

BY

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It is recognized that heart block may occur in several acute infections, but apart from diphtheria and acute rheumatism it is rare and even in the latter it is uncommon. Often the outcome of this complication in children is fatal, but in the following case, a boy aged 12, with heart block and pericarditis, recovery took place.

For three months before admission to hospital he had felt tired and had to rest on returning from school. He had been restless for the past few nights and eventually had to remain in bed for three days. During this time he had throbbing of his heart and headache. For two days he had a troublesome unproductive cough, and on the day before admission he had two attacks of unconsciousness. On coming round he perspired and vomited. He had one attack of unconsciousness the day before coming to hospital and on admission he complained of giddiness, shortness of breath, and persistent coughing. Apart from measles there was no history of any previous illness.

On admission the patient was very ill. He presented grey cyanosis and was distressed by severe dyspnoea. The temperature was normal and the pulse was small and 160 a minute. The blood pressure was 80/40. The respiration rate was 44. There was prominent pulsation and distension of the cervical veins. The apex beat was diffuse and was just outside the mid-clavicular line. The heart sounds were distant and the second sound was split and accentuated in the pulmonary area. There were no murmurs. Numerous rales were heard over the chest. No other abnormal sign presented on further examination; there was no distension of

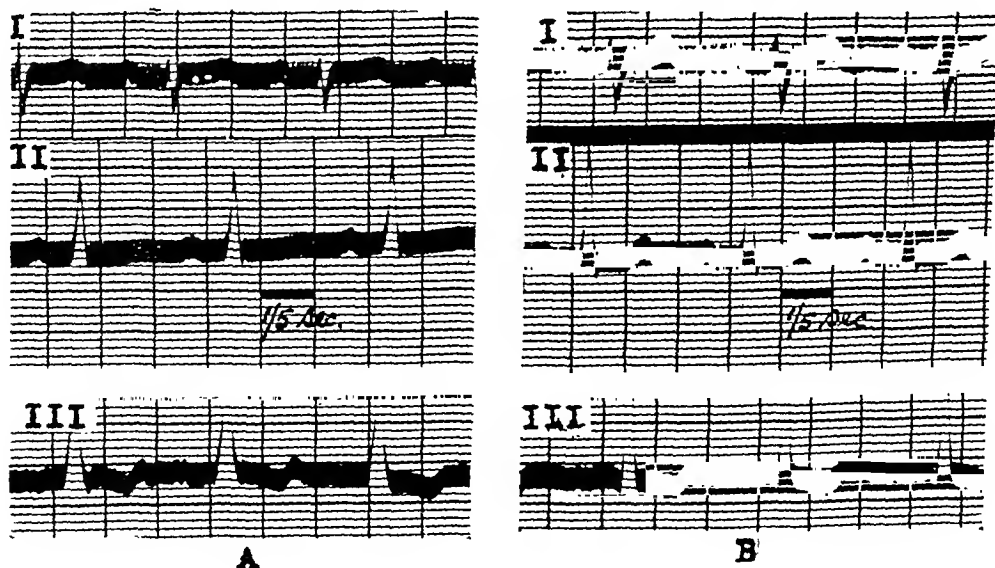


FIG. 1.—Electrocardiograms. (A), taken two weeks after admission, shows flat T waves in lead II and inverted T waves in lead III; (B), taken six weeks later, shows an upright T wave in lead II.

liver and no ascites or œdema. The diagnosis of acute rheumatic pericarditis was considered likely. The patient's general condition deteriorated and he was given oxygen by nasal catheter. Next day the pulse rate dropped to 48. The diastolic blood pressure rose to 70 but the systolic was difficult to record. On the morning after admission, I witnessed two Stokes-Adams attacks. They were preceded by restlessness, an anxious expression, complete irregularity of the pulse, and quick and deep breathing. The pulse, the heart sounds, and later the respiration, ceased. Pallor gave way to cyanosis. There was no twitching. No pulsation of the vessels of the neck was observed during the cardiac standstill. Unconsciousness lasted for ten seconds. After coming round the patient became very flushed and perspired profusely. He was given ephedrine and digitalis and the pulse remained at 80 to 90.



FIG. 2.—X-ray of chest one day after admission to hospital.



FIG. 3.—X-ray of chest eight weeks after admission to hospital.

During the next three days he had further attacks, but these became less frequent and the patient improved. A pericardial rub appeared on the third day and lasted for three days. At no time did he have any pyrexia or œdema and his later recovery was uneventful. His blood pressure rose to 110/70 and his pulse remained regular at 90. No electrocardiogram was taken during the period of irregularity and later it showed changes due to pericardial effusion with a normal P-R interval (Fig. 1).

Radiography also confirmed the pericardial effusion (Fig. 2 and 3).

DISCUSSION

It is known that primary carditis in childhood is often the first and only manifestation of rheumatic infection. Though Cheadle (1889) and later Moore (1909) stated that carditis was the central factor in rheumatic infection in childhood the diagnosis was often impossible owing to the absence of specific symptoms. In my case the pericarditis was probably rheumatic in origin and its presence was confirmed by the pericardial rub and later cardiographic and cardioscopic findings.

According to Lewis (1925) the cause of clinical heart block is firstly a lesion of the conducting tract, secondly vagal stimulation, or thirdly the result of poisoning. The first cause was operative in my case and the evidence points to heart block caused by rheumatic infection. It is obvious that this infection must have involved the myocardium and the pericardium but there was no evidence of endocardial involvement. The recovery of the patient precluded any pathological examination of his tissues, but certain conclusions can be drawn from the

clinical examination. In the cases that have come to necropsy there have usually been found inflammatory infiltration with rheumatic giant cells and fibrotic changes. In some cases there has only been exudation in the collagenous tissues of the membranaceous septum. Gross and Fried (1935) in 110 necropsies on rheumatic hearts frequently found inflammatory changes in the collagenous extension of the fibrous septum which abuts on the bundle tissue. In many of their cases a portion of the conducting system was entirely surrounded by relatively rigid collagenous tissue and they considered that this, when expanded by exudation, might compress the conducting fibres. It seems reasonable to suppose that in my case as there was no permanent lesion of the conducting system, the pathological change was in the nature of either a minor inflammatory condition of the bundle tissue itself or of such exudation which pressed on the bundle.

SUMMARY

A case of insidious rheumatic pericardial effusion with Stokes-Adams attacks is described. A boy of 12 sought medical help after three months of ill health and only when disturbance of the conducting system had set in. Either minor inflammation of the bundle tissue itself or its compression by inflammatory vascularization of the collagenous mass in the septum membranaceum, would explain the symptoms.

I should like to thank Dr. Fiddes, Medical Superintendent, E.M.S. Hospital, Billericay, Essex, for facilities and Dr. William Evans for helpful advice.

REFERENCES

- Cheadle, W. B. (1889). *Lancet*, 1, 821.
Gross, L., and Fried, B. M. (1936). *Amer. J. Path.*, 12, 31.
Lewis, T. (1925). *The Mechanism and Graphic Registration of the Heart Beat*, 3rd ed., London, p. 183.
Moore, N. (1909). *Lancet*, 1, 1159.

COMPLETE HEART BLOCK

BY

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This paper discusses 64 cases of heart block, mostly complete, seen during the same period as 29 cases with dropped beats and 140 cases with latent heart block (Campbell, 1943, *b* and *c*).

Of the patients attending the Cardiographic Dept., Guy's Hospital, during 12 years, 0.6 per cent had complete, 0.5 per cent partial, and 2.2 per cent latent heart block. Comeau (1937) found 0.55 per cent of cardiovascular cases had complete block; and Paul White (1937) found 0.8 per cent had complete, 2.6 per cent partial, and 3.0 per cent latent. It is curious that with such close agreement between the other figures he should have found so many more with partial block.

An analysis of the age and sex of the cases and of their aetiology was similar to that found in other series, so this and the clinical features will be dealt with shortly. Three aspects will be dealt with rather more fully—the prognosis, the incidence and significance of Stokes-Adams attacks, and the extent to which complete block remains persistent or varies to lower grades of partial or latent block. This leads to a more complete classification of the subdivisions of heart block.

I had the impression that, apart from the cases in hospital with frequent changes of rhythm and Stokes-Adams attacks, complete heart block was as a rule persistent once it had been found. But half my cases had more than one grade of heart block graphically recorded; and more than 60 per cent were observed clinically to have such changes. Sometimes these were frequent and one did not know with what rhythm the patient would be seen next: sometimes, after a long period of complete block, partial or latent block was seen for no apparent reason.

AETIOLOGY

Sex incidence. There were 51 men and 13 women, a preponderance of 4:1. If the 3 rheumatic cases (all women) were excluded the proportion rose to 5:1. Graybiel and White (1936) found the proportion 2:1; and all observers are agreed that it is much more common in men.

This is another contrast between complete and lower grades of heart block where the difference of sex incidence is absent or much less marked. In my 38 cases with dropped beats, 19 were men and 19 were women, and this applied as much to the elderly myocardial group as to the younger patients with rheumatic and other infectious diseases. In the 31 cases with latent block with a P-R interval over 0.26 sec. or more there was a preponderance of males, but it was entirely in the elderly group. There were 19 younger patients (average age 24) with rheumatic and other diseases, and here there were 11 males and 8 females: there were 12 older patients with myocardial disease (average age 56), and here there were 10 men and 2 women—the same proportion as with complete block.

Age incidence. The age, reckoned from when they were first seen (and generally this seemed to be near the time of onset), is shown below.

| | | | | | | | | |
|-----------------|----|----|----|----------|----------|----------|----------|-------------|
| Age | .. | .. | .. | Under 40 | 40 to 49 | 50 to 59 | 60 to 69 | 70 and over |
| Number of cases | .. | .. | .. | 5 | 5 | 17 | 29 | 8 |

Most patients (45 per cent) were between 60 and 69, and 84 per cent were over 50. In the small number under 40, the prognosis seemed to be better, but otherwise the age did not seem to be important. The better prognosis at the younger age would, of course, be made much more striking had congenital cases been included. A more detailed analysis is given in Table I. Originally those with and those without latent block were listed separately, but as there was no significant difference they have been combined.

TABLE I
AGE OF PATIENTS WITH HEART BLOCK (AGE WHEN FIRST SEEN)

| | Under 40 years | 40 to 44 | 45 to 49 | 50 to 54 | 55 to 59 | 60 to 64 | 65 to 69 | 70 to 74 | 75 and over | Total |
|---------------------------------------|----------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|-------------------|-------|
| Patients known to have died .. | 1 | 2 | 2 | 3 | 4 | 8 | 7 | 5 | 2 | 34 |
| Patients still alive when followed .. | 4 | — | 1 | 1 | 3 | 4 | 3 | — | — | 16 |
| Patients not traced | — | — | — | 4 | 2 | 3 | 4 | 1 | — | 14 |
| Total | 5 | 2 | 3 | 8 | 9 | 15 | 14 | 6 | 2 | 64 |

Ætiology. Myocardial disease without any evidence that it was rheumatic or syphilitic was much the most common cause—86 per cent of all cases, or 76 per cent if congenital cases were included. The congenital cases, which have been excluded otherwise from this paper as they have already been reported (Campbell, 1943*a*), were the second commonest group, forming 13 per cent of the total, while the rheumatic and syphilitic groups together formed only just over 11 per cent.

The figures found in the series collected by Graybiel and White (1936) were so similar that I have included them for comparison in Table II. The only significant differences were that they have included a few cases in a diphtheritic group, of which I have not found any examples, and had left more cases as due to combined causes (where I had more dogmatically placed the case in one group or the other according to the factor that seemed most important), and that I had more congenital cases. The average ages of the different ætiological groups have also been added.

TABLE II
AETIOLOGY OF COMPLETE HEART BLOCK

| Aetiology | Number of cases | | Average age | |
|-------------------------|-----------------|--------------------|-------------|-------------------|
| | This series | Graybiel and White | This series | Graybiel and Whit |
| Rheumatic | 3 | 3 | 34 | 41 |
| Syphilitic | 5 | 3 | 42 | 43 |
| Myocardial | 56* | 47 | 64 | 63 |
| Congenital | 10 | 4 | 4 † | 6 |
| Diphtheritic | 0 | 4 | — | 35 |
| Combined causes | 0 | 11 | — | — |
| Total | 74 | 72 | — | --- |

* High blood pressure, 10; coronary atheroma, 17; cardiac failure, 4; and cardiac enlargement generally with atherosclerosis without the previous features, 25.
† The present age of the seven known to be alive is 30 years.

High blood pressure has not been taken as a separate main division and my evidence for calling a case myocardial must be given. Of the 56, 10 had high blood pressure (over 160/100). In several others the systolic pressure was high, but as this seems to rise in many—but by no

means all—cases to compensate for the long diastole, this was not counted until the diastolic pressure was also raised; 17 were included as having coronary arterial disease and the evidence for this was a history of angina pectoris or cardiac infarction; and 6 had congestive heart failure without high blood pressure or evidence of coronary disease.

The remainder had enlargement of the heart without these other findings: it is surprising that cardiac enlargement was the only other decisive evidence of heart disease in 23 of the 56, though many had thickened radial or retinal arteries and still more had signs of atherosclerosis of the aorta on radioscopy. It is surprising and significant that so many patients with complete heart block seem relatively well and are able to lead quiet lives, almost normal for their age, provided they do not suffer from Stokes-Adams attacks. One common type is the elderly man with grey hair and thickening arteries who has led a strenuous and sometimes intellectual life, often with hardly a day's illness.

The rheumatic cases were few: one with mitral disease had varying grades of heart block that were occasionally complete (Case 107, p. 80), one had temporary block during active rheumatic carditis (Case 113, p. 83), and one was called rheumatic on a history of rather doubtful rheumatism in childhood (Case 140, appendix). Their average age was 34 years. Perhaps a fourth should have been included, but on his age of 68, on the late onset of any symptoms before his congestive failure, and on the signs being predominantly those of aortic stenosis, he was included as atherosclerotic though he had also some aortic incompetence and a history of rheumatic fever 38 years before (Case 150). The two other cases with aortic stenosis are referred to on p. 76.

Case 150. A man, aged 68, had rheumatic fever when he was 30. He got on well, though with increasing dyspnoea as he got older, till at 68 he was admitted to hospital with congestive heart failure. He was found to have aortic stenosis and incompetence, C.H.B., B.B.B.I., and auricular fibrillation (Fig. 1); his B.P. was 190/60; his W.R., negative. He improved for a time but died five months

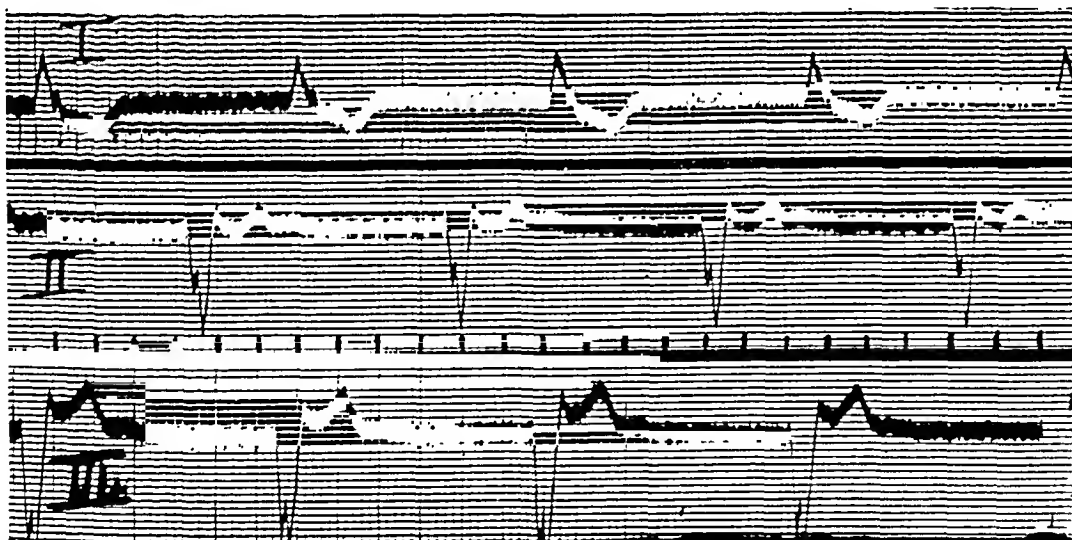


FIG. 1.—A faster rate than usual, in an old man with atherosclerosis and aortic stenosis. His rate averaged 48 and was 47 a minute in this record, when he had also, as usual, bundle branch block and auricular fibrillation (Case 150). In this and most subsequent figures the inked marks indicate 1/5th sec.

later, after developing coupled beats of an irregular type, probably as the result of treatment with digitalis (Fig. 2). Post-mortem, there was left ventricular hypertrophy with extreme calcification of the coronary arteries. There was calcified thickening of the aortic cusps and old fibrosis of the mitral valve.

The striking thing about the syphilitic cases was that none had the usual signs of aneurysm or gross aortic incompetence. One only had a slight aortic leak and he gave no history of syphilis and had a negative Wassermann reaction (W.R.) (Case 123, appendix). One was

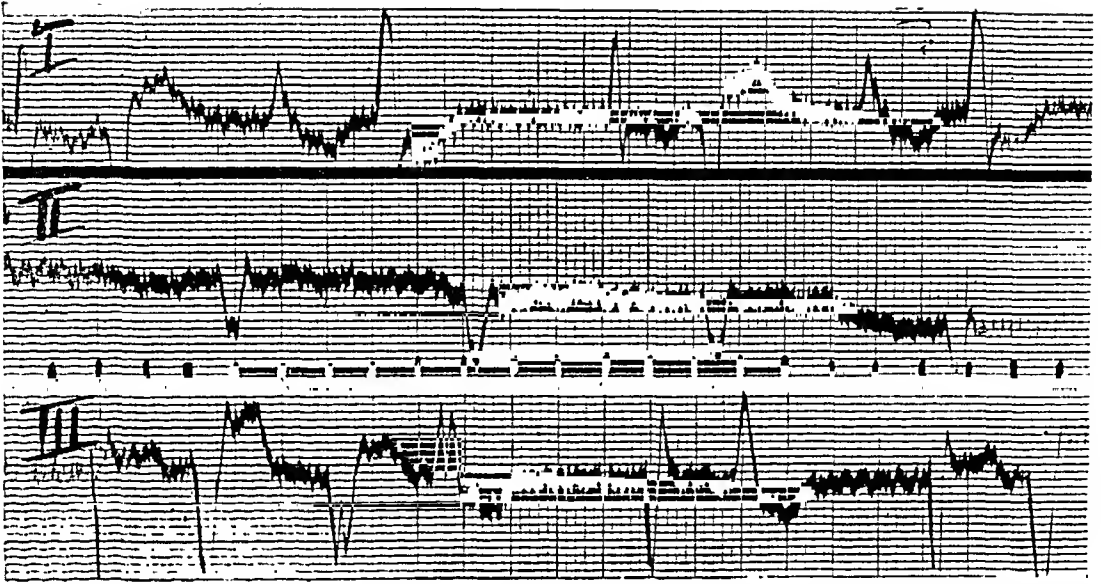


FIG. 2.—Bigeminy of an irregular type from the same patient as Fig. 1. It was taken some months later, shortly before his death, and may have been partially due to digitalization. In lead II there is C.H.B. with a still faster rate of 54 a minute; in leads I and III, bigeminal extrasystoles of different types and also changes in the bundle conduction.

included on a positive W.R. and signs of neurological syphilis though his blood pressure was 250/130 (Case 101, p. 83). One was included on a positive W.R. only (Case 138). One may have had congenital syphilis as her father had died with general paralysis of the insane, but there were no other signs of this and her W.R. was negative (Case 159, appendix). The last, aged 34, was included on the sole evidence of a weakly positive W.R. (Case 108, p. 81). The average age of these five patients was 42. Even in these cases it will be agreed that it was not really certain that the heart block was caused by syphilitic disease.

There were three others where this diagnosis had to be considered. One had a positive W.R. but also had a blood pressure of 210/130 and albuminuria, and post-mortem his heart weighed 900 g. and there was no evidence of syphilitic disease (Case 120, p. 81). Two others had angina and arteriosclerosis and were classified as this, although one had a positive W.R. (Case 104) and the other a history of syphilis with a negative W.R. (Case 119), because there was no evidence on radioscopy or otherwise of syphilitic disease.

A possible explanation of the absence of typical syphilitic cases is that these develop in the quaternary stage of the disease, and that heart block, when it is syphilitic, is more likely to arise in the tertiary stage as the result of a gumma affecting the A-V bundle.

There is unusual doubt about how many of these cases should be included, but if every doubtful case were included as rheumatic or syphilitic the incidence would only be increased to 5 and 10 per cent respectively.

STOKES-ADAMS ATTACKS

Stokes-Adams attacks are found in about half the patients who attend hospital with complete heart block, and probably this gives a true picture of their incidence. When present they form the most striking part of the clinical picture. They may be few and far between, or very frequent, or frequent at first and rare or absent later.

The patient who has not had an attack when first seen need not, however, be unduly alarmed about them. Probably he will never have an attack, and after six months freedom, their onset becomes much less likely (see p. 74). His outlook must therefore be judged on the presence of congestive failure, angina pectoris, etc. Except for the statistical evidence

that follows I have no help to give for the prognosis of those who have these most alarming and unpredictable attacks.

It is not easy to decide exactly what should be included as Stokes-Adams attacks. Should the minor attacks in which consciousness is not lost be included, as these are obviously due to the same mechanism but of shorter duration? Should similar attacks in patients without heart block be included? In order to give a precise meaning to the term, I think they should not and would accept the definition of Parkinson, Papp, and Evans (1941): attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these, in a patient with heart block. It is most important to add that the heart block may be established or paroxysmal, and as the paroxysmal heart block may only occur for a short time after the attack, the diagnosis must sometimes be made on clinical grounds only without a proof of the heart block when no precise record of the behaviour of the heart during and after the paroxysm is available. The attacks are of two main forms, syncope or epileptiform, this probably depending on the duration of the arrest of the heart's action.

It is sometimes thought that the onset must be absolutely sudden, as it obviously is in most patients who fall so that they hurt themselves. But in some patients a shorter arrest of the heart's action—too short to produce a true attack—would produce a feeling of faintness and other symptoms; and in such patients these symptoms will often be present as an aura to the fully developed attack. By chance the first two patients quoted by Parkinson *et al.* illustrate these two possibilities, and we have many examples.

Case 4 of Parkinson *et al.* proves, if further proof were needed, that the minor attacks are of the same nature. After various symptoms "he expected to faint but only turned pale and breathed rapidly. In some of them the pulse stopped and the ventricles ceased beating for 5 seconds or more." . . . "In almost as many attacks consciousness was lost and the ventricular standstill lasted 10–20 seconds, the patient becoming unconscious towards the middle of this period."

This paper of Parkinson, Papp, and Evans has dealt so fully with the actual behaviour of the heart during the attacks that I have nothing to add except a description of one case of Dr. Suzman's (see appendix). But in most cases cardiographic records are not available and the diagnosis must be made on the story. Generally there is not much difficulty in patients with the classical abrupt onset who fall and hurt themselves, unless the heart block is missed because it is paroxysmal. But the preliminary aura may lead to confusion with fainting attacks, vaso-vagal attacks, or even hysteria, though the sensible matter-of-fact patient generally prevents this.

The aura may be very variable and a few random examples are given in the patients' own words. "Can't breathe, pins and needles all over the body, then remember nothing" (Case 107). "Feel rushing in the ears, then dazed for a few seconds, then trembling, then all right again—would fall down if I had nothing to hold, and can sometimes remember the actual fall" (Case 108). "Go blind, feel queer and giddy *and as though my heart has stopped*, and then fall down unconscious" (Case 130). [I have put some of these words in italics because I think that many patients are remarkably aware of visceral happenings, and that some doctors are not ready to pay enough attention to the patient's description of his sensations, on which most of our diagnosis rests.] "Severe precordial pain passing up the left side to the lower angle of the jaw, then fall unconscious" (Case 142).

Case 123 (appendix) gave a most curious story and no diagnosis was made for years; even when he developed heart block I did not feel sure of the nature of his attacks which were probably associated with paroxysmal heart block at first, until I had become more familiar with this condition.

It is sometimes said that biting the tongue and incontinence of urine or fæces are diagnostic of epilepsy and exclude Stokes-Adams attack. This is not so, though these events are rare

in Stokes-Adams attacks and common in epilepsy. In Case 7 of Parkinson *et al.* there was incontinence of urine and in Case 6 incontinence of fæces. The occurrence of tongue biting and incontinence of urine in my Case 142 can not therefore establish the original diagnosis of epilepsy that was made in this patient. Probably the duration of the ventricular standstill is the decisive factor.

Minor attacks. Between true Stokes-Adams attacks and the attacks of faintness and giddiness that are not included as such, there are minor attacks which have the same relationship to true attacks as petit mal to grand mal. Case 116 provided a good example. In one major attack he "felt it coming, but had no time to get to the railings and fell and cut his head." In a minor attack he "felt a little funny on his way home from work, had a momentary blank, but the paper did not fall from under his arm."

It is not easy to see why there should be such a variety of symptomatology. In epilepsy the varying auras can be explained by different spreads of the nervous impulses through the brain, but in Stokes-Adams attack the heart is at fault and one might guess the central effect in the brain would always start and spread in the same way. But patients with Stokes-Adams attacks have generally atherosclerosis, and probably different degrees of atheroma in different cerebral vessels influence the effect that ventricular standstill has on the functions of the brain.

Presenting symptoms. There was a striking difference in the presenting symptoms of those with and of those without Stokes-Adams attacks. Most of the latter were first seen for dyspnœa or attacks of faintness or giddiness.

Of the former, 21 (63 per cent) were first seen because of the Stokes-Adams attacks and they had no serious cardiac symptoms before this. It does not, of course, follow that the attack was actually at or near the onset of complete heart block (C.H.B.) but it seems likely that this was so in many cases; 2 others had coronary thrombosis which was quickly followed by C.H.B. and Stokes-Adams attacks, though in one of these the slow pulse was noted the day before the first attack.

There were, on the other hand, 8 cases where the heart block was known to have been present for a reasonable period before there was a true Stokes-Adams attack: 6 of these had attacks of faintness or dizziness as the first presenting symptom, 1, 1, 3, 4, 8, and 24 months before respectively ("last two years have had several giddy turns, too many to count; last week fell and cut my head", Case 116); one other complained of dyspnœa only and 6 months later had his first attack, and the eighth came to hospital for gangrene of his leg and had his first attack 7 weeks later.

The remaining 2 cases were under observation for dyspnœa and angina before they developed C.H.B. The former was readmitted to hospital with congestive failure and C.H.B. and the first attacks which soon proved fatal followed 5 months later (Case 120). The latter was found to have C.H.B. five weeks after her first Stokes-Adams attack and as this was the first time she had been seen since the attack it probably indicated the origin of the C.H.B. (Case 118, p. 81).

Thus the Stokes-Adams attacks were the first significant symptom of C.H.B. in 72 per cent; and in 27 per cent the C.H.B. was known to have been present, or other symptoms made this likely, for an average period of 6 months before there was a Stokes-Adams attack.

The exact onset of complete heart block is often unmarked by any specific symptom where the patient does not suffer from a Stokes-Adams attack. In certain patients, however, it can be recognized, and I have three histories where there was some confirmatory evidence. "Sudden thumping in the ears, nearly lost control, but was not unconscious"; his doctor found the slow pulse the same afternoon (Case 134). "Started with onset of giddiness, nearly fell down, noticed breathlessness the same day" (Case 162). "Attacks of flushing, giddiness, and discomfort, without loss of consciousness, starting when my heart became

slow." This should be accepted, as after six years of established complete heart block she came to hospital one afternoon saying that her heart had gone back to its normal rate and this was found to be the case (P-R, 0.23 sec.), but it did not persist: high blood pressure may have made her unusually aware of her heart rate (Case 125). Of the 31 who had not Stokes-Adams attacks, dyspnoea (10 cases) or faint or giddy attacks (12 cases) were almost equally common presenting symptoms, and between them accounted for 70 per cent of the cases. Of the others, three had congestive failure, one angina pectoris, and one coronary thrombosis. In the remaining four the presenting symptoms were varied and often non-cardiac and the finding of complete heart block was a surprise.

OTHER FEATURES OF THE CLINICAL PICTURE

Heart rate. This was carefully analysed in 30 patients in whom I had frequent records over a reasonably long period—sometimes for many years. Taking an average figure for each case, the results are shown in Table III.

TABLE III

HEART RATE IN COMPLETE HEART BLOCK

| Heart rate | Under 24 | 24 to 27 | 28 to 31 | 32 to 35 | 36 to 39 | 40 to 43 | 44 and above |
|--------------------|----------|----------|----------|----------|----------|----------|--------------|
| Number of cases .. | 1 | 3 | 6 | 4 | 9 | 5 | 2 |

In the great majority the average rate was between 28 and 40 with a grand average of 34.6 a minute. This is slower than the rate of 38–40, given by Graybiel and White (1936) and I think more in accord with general experience. Of course there was variation in an individual case from time to time, and typical figures were 24–30, 28–36, 32–40, and 36–42; in the two patients in whom there were the largest number of observations over many years, the range was 32–44 with two single readings of 45 and 54, and 28–40 with an average figure of 34.8.

The specially fast and slow rates were considered for all the patients. Two had average rates of 24 (Cases 144 and 146) and both were specially liable to feeling faint and giddy apart from their true Stokes-Adams attacks. One, who died three days later in a Stokes-Adams

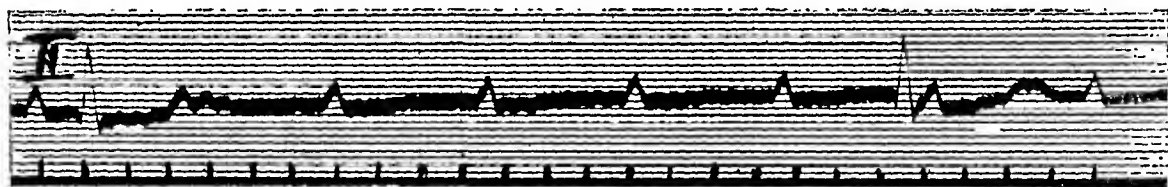


FIG. 3.—An unusually slow rate in complete heart block. His rate, clinically, was often 18–20 and here in lead I it was as slow as 15.8 a minute (Case 155).

attack, had a rate of 18–20 and sometimes a cardiographic rate of 17 (Fig. 3); curiously enough he did not complain specially of any symptoms while this record was taken (Case 155).

In several patients a slower rate than their usual one was often associated with regular bigeminal ventricular extrasystoles (Fig. 4) and was perhaps their cause, though it is not clear how they arise in complete heart block. For example, one whose rate was generally 32–44 had a rate of 56 with alternating extrasystoles, i.e. a true rate of 28; and another whose usual rate was 28–40 had alternating extrasystoles when the rate without these would have been 22.

Rates over 44 were rather more common but there were special features about the four patients in whom these were found regularly at rest. A girl, aged 18, is reported in the appendix (Case 159). In a young woman, whose heart block was temporary and due to acute rheumatic carditis, the rate was 62 (auricle 115) (Case 113, p. 83); this rapid rate with complete heart block is well known in diphtheria.

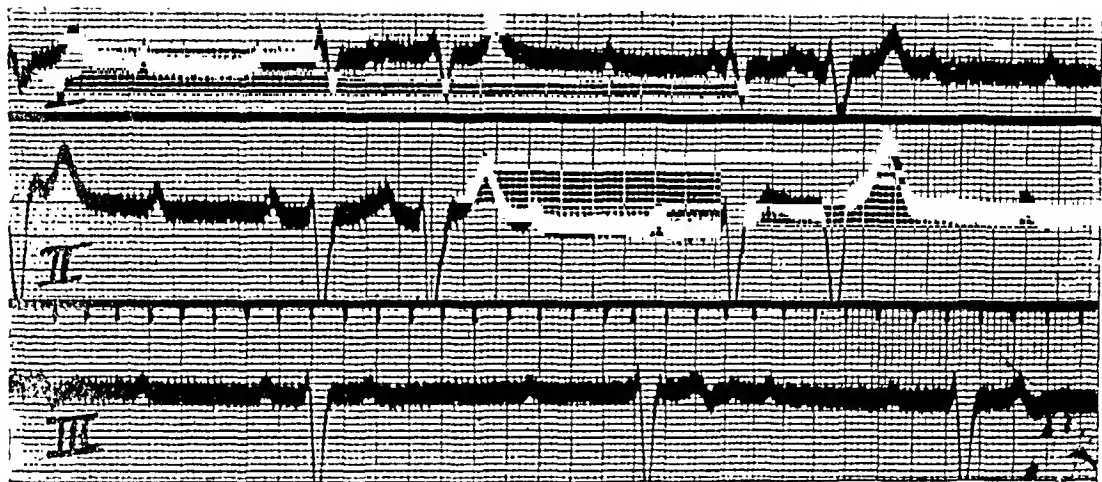


FIG. 4.—Regular bigeminal extrasystoles with complete heart block. In lead III the ventricular rate is a little faster and there are no extrasystoles (Case 132).

In two cases with aortic stenosis and incompetence, the rate was between 36 and 50 in Case 126 (p. 81), and in Case 150 (p. 71) it averaged 48. These suggest that with aortic stenosis the rate tends to be faster, but in the only other patient with aortic stenosis, a man of 63 with high blood pressure, the rate was 34–42 (Case 102, p. 81). All these three had B.B.I. also.

Heart rate after exercise. It is generally thought that there is not much change in the heart rate with exercise in cases of complete heart block. Often this is true, at any rate with the gentle exercise they are able to take, and the rise is no more than a few beats a minute. Case 108, for example, showed very little increase even when the auricular rate was doubled. At the other extreme Case 159 showed an increase from 46 to 60 and sometimes to 70 (details are given in the appendix). In congenital complete heart block, where seven cases were tested, I found an average increase from 48 to 55, or to 64 if the rate was calculated from the first quarter-minute only. Even in some of the elderly patients with atherosclerotic complete heart block there may be considerable increases, e.g. in Case 132 the rate was increased from 38 to 58 a minute. Here there was also a change in the type of ventricular complexes (Fig. 5 and 6), but this is, of course, not usual. In the patients with varying degrees of heart block the result of exercise was not easy to foretell. In Case 142 with 2:1 block the auricular rate

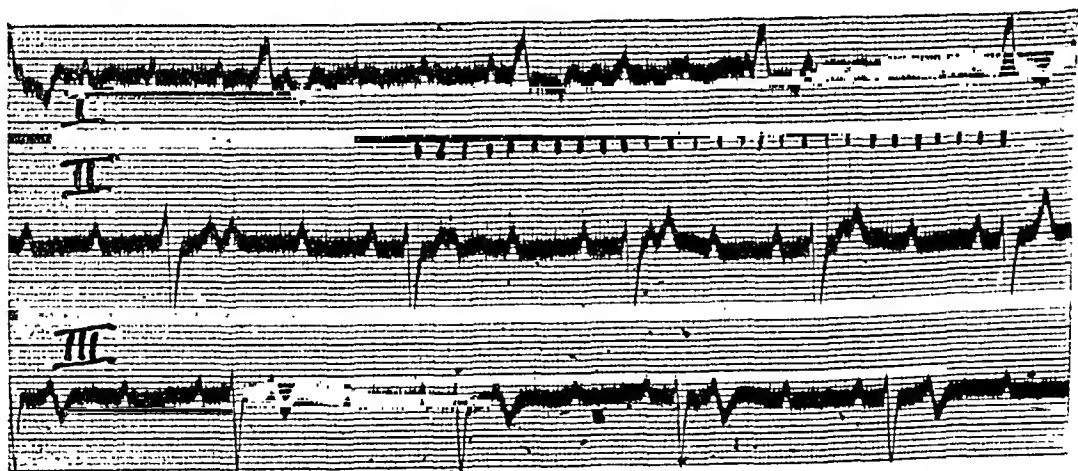


FIG. 5.—Complete heart block with a ventricular rate of 38 from a man, aged 59, who was under regular observation for five years. His B.B. was 200/100 and his W.R. was negative. He had five Stokes-Adams attacks in the first two years, but after taking pot. iod. regularly was three years without an attack except once when he had stopped it for 6 weeks. (Case 132, see also Fig. 6.)

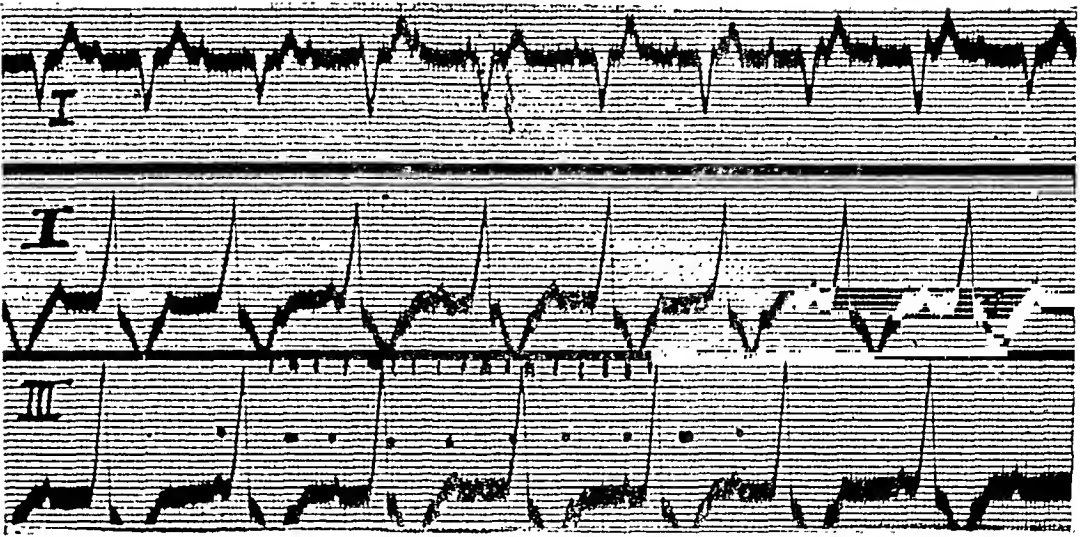


FIG. 6.—Complete heart block from the same case as Fig. 5 with a much faster ventricular rate (58) and a change in the ventricular complexes after exercise. This change was produced on several occasions with exercise (Case 132).

was increased from 70 to 124 while 2 : 1 block was still maintained. In Case 145, 2 : 1 block before exercise changed to complete block after it, but on another day complete block before exercise changed to 4 : 1 block after it.

The blood pressure. The cases were classified as hyperpietic where the systolic pressure was over 160 and the diastolic over 100. In these 10, the average blood pressure was 225/108. This is a high pulse pressure as more common averages for ordinary cases of hyperpiesis would be 225/130 or 180/108.

Of the much larger number of cases not falling into this classification of high blood pressure, there were by chance almost exactly equal numbers with a systolic pressure above and below 160. In the former the average figure was 194/81 and in the latter 137/73. Roughly speaking one could say that in half there was a high pulse pressure (about 100) and a high systolic pressure with a normal diastolic pressure, and that in half all three were normal, perhaps with a slightly raised pulse pressure. A more detailed analysis, putting the cases into eight equal groups according to the height of their systolic pressure, gave the following average figures: 224/82, 195/86, 187/80, 169/75, 150/81, 141/77, 134/70, and 121/65.

The slow forceful heart beat with its long diastole has been said to produce a high systolic pressure to maintain the circulation adequately and, with more certainty, some fall in the diastolic pressure. This is no doubt part of the explanation but does not seem to be the whole, as half the cases showed so little increase of pulse pressure. Possibly, for this reason, some additional cases should be classified as hyperpietic, because originally they had a higher diastolic pressure, i.e. above 100, but we have no direct evidence of this having happened except perhaps in Case 142 where an early pressure of about 170/97 seemed to have settled at 235/88 six years later.

Probably a more important factor is the atherosclerosis of the aorta that is such a marked feature of many of these cases, though not to a greater extent than in many elderly men. Although several writers have pointed out that as the aorta becomes less elastic a greater pulse pressure is needed to stretch it enough to accommodate the same stroke volume with each heart beat, the significance of this as a cause of a high systolic and high pulse pressure is still insufficiently recognized. It follows from the known physiological facts that the systolic pressure must rise greatly as the elasticity of the aorta diminishes, if the output of the heart is not to fall. This automatically increases the work of the heart. In many elderly patients the diminished output, the increased systolic pressure, and the increased work of the

heart in stretching the aorta are all factors in diminishing the capacity for effort quite apart from any rise of diastolic pressure due to true hyperpiesis which would further accentuate the difficulty.

Bundle branch block. There was some association between bundle branch block (B.B.Bl.) and the lower grades of heart block, nearly 4 per cent of those with latent block having B.B.Bl. There is a closer association between B.B.Bl. and complete heart block. Of the 64 cases, 13 had typical, and 6 others somewhat atypical, B.B.Bl., the combined figures being nearly 30 per cent; in addition another 8 had widened QRS complexes that did not amount to B.B.Bl. In a few cases the B.B.Bl. was irregular, being sometimes present and sometimes absent. In some who had both latent and complete block, there were various findings: B.B.Bl. with C.H.B. and not with N.R. (Case 126, see Table VI), B.B.Bl. with N.R. but not with C.H.B. (Case 111, see p. 84), or B.B.Bl. sometimes with C.H.B. and sometimes with

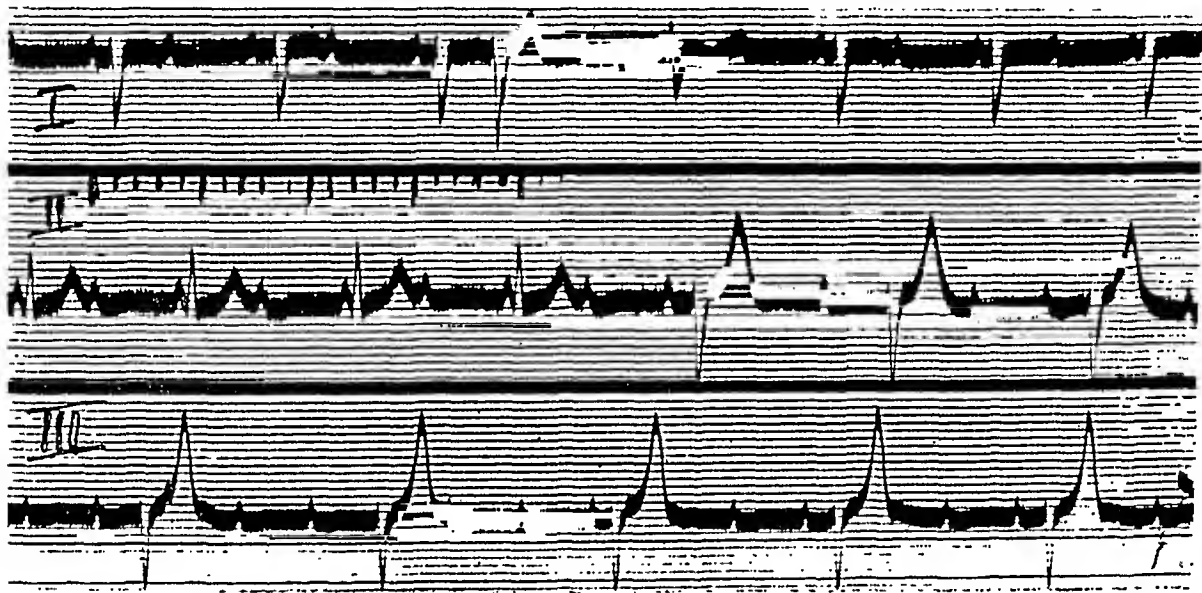


FIG. 7.—Complete and 2 : 1 heart block in a man, aged 60, in whom such changes were frequent. Here the abnormal ventricular complexes came when the block was complete, but this was not always so (Case 131). He had frequent Stokes-Adams attacks and died a year later.

N.R. (Case 102, see p. 81). Fig. 7 illustrates a change in the ventricular complexes when the degree of block changed from 2 : 1 to complete.

All the three patients with aortic stenosis and C.H.B. had B.B.Bl. also.

PERSISTENCE OR CHANGE IN THE DEGREE OF BLOCK

Complete heart block may continue from the time it is first observed until the patient's death. In many cases, however, there are frequent or occasional changes, and different grades of block are observed from time to time. The change may be only to partial block or to latent block, or even to normal rhythm with a normal P-R interval. All cases, except those with congenital complete block, have of course had normal rhythm earlier but this is not included; a few may have had latent block for some time before complete block developed, but the small numbers in whom this sequence of events was observed show that it is not common. It is not easy to classify the different combinations of these changes. This is mainly because of their variety, but partly because the patient is only under close observation for a relatively short time.

Before discussing the changes found in this series of cases the various possibilities will be set out more fully. Complete heart block may be *established* when that rhythm is per-

sistent from the start. It may be *varying*, when complete, partial, or latent block follow one another from time to time. It may be *varying becoming established* when changes are present at first but do not persist. This is a form of progressive heart block but certain cases with a more regular increase in the degree of block have been considered as a special sub-division, *progressive* heart block. It may be *remittent* or *interrupted*, when partial or latent block occasionally interrupts complete block. These remissions may come after a period of years when complete block was present each time the patient was seen and had appeared to be established; in others they are more frequent and it may be difficult to draw the line between this and the *varying* group. All these changes are found in patients who have no Stokes-Adams attacks as well as those who have. In all these groups complete heart block is either the dominant or at least a common rhythm.

There are also cases where complete block is the unusual or temporary rhythm and these can be usefully divided into two groups. It may be *transient*, when it follows cardiac infarction or an acute infection and only lasts during this; or *paroxysmal*, when it occurs without such a known cause. In connection with these cases previous views about paroxysmal heart block will be shortly discussed. The present series of cases will now be considered to see how they fit into the suggested classification.

The details of the changes that were recorded are set out in Table IV. In 29 cases all records taken showed complete heart block, in 3 all showed 2:1 block, and in 4 both these rhythms but no other. Another 28 * cases showed complete and/or 2:1 block and at other times latent block only, 15 of these having complete block, 2:1 block, and latent block at different times.

TABLE IV
GRADES OF HEART BLOCK

| | Latent block (total) | Dropped beats (total) | 2:1 H.B. (total) | C.H.B. (total) | Stokes- Adams attacks | Total number of cases | Corrected figures using clinical evidence also † |
|---|----------------------------|-----------------------------|---------------------|-------------------|-----------------------------|-----------------------------|---|
| C.H.B. only | — | — | — | 29 | 14 | 29 | 23 |
| 2:1 H.B. only | — | — | 3 | — | — | 3 | 2 |
| 2:1 H.B. and C.H.B. .. | — | — | 4 | 4 | 4 | 4 | 4 |
| C.H.B. and latent block | 6 | — | — | 6 | 4 | 6 | 13 |
| C.H.B., 2:1 H.B., and latent block | 15 | 6 | 15 | 15 | 6 | 15 | 18 |
| 2:1 H.B. and latent .. | 7 | 3 | 7 | — | 5 | 7 | 4 |
| Latent block with dropped beats only | 29 | 29 | — | — | 2 | 29 | |
| Latent block only .. | 140 | — | — | — | 1 | 140 | |
| | 197 | 38 | 29 | 53 | 36 | 233 | |

† For the rest of the table the grade of heart block had always been proved by graphic records.

Established heart block. At first sight the group of 29 cases with complete heart block (C.H.B.) only might suggest that this rhythm generally persists without change. On examination, however, the proportion had to be reduced somewhat. In 8, few cardiograms were taken because the patients were not seen frequently or did not live long. In 6, faster heart rates of about 60–70 were often observed in the ward, but as they always had C.H.B. when graphic records were taken it is not known if they changed to normal rhythm or to latent block or sometimes to 2:1 block. All 6 had Stokes-Adams attacks. In 5 of them the changes

* Case 58, included in my previous paper as latent block only because this was the only rhythm proved graphically, has here been accepted as complete block also since the clinical evidence for a higher grade of block was good.

were frequent; and 3 of these died in less than a year. In the sixth the changes were frequent for three months but in the last six months of his life the rhythm seemed always C.H.B. and he had no more Stokes-Adams attacks.

In the remaining 15, frequent cardiograms were taken more or less regularly, and so far as we know the block was always complete at all other times as well. Of these, 8 died after 1-7 years, and 7 were alive when last heard of after 3-20 years. The classification of these cases would, therefore, be: established 15; varying 5; and varying becoming established 1.

Varying heart block. There were 4 cases with complete and 2 : 1 block. In 3 the changes were frequent but 2 were not under observation for very long; and in 1, the rhythm was generally 2 : 1 during the first few months but later became established C.H.B. for 12 years (varying, 3; varying becoming established, 1).

The 28 patients with complete, partial, and/or latent block must next be considered, and some details are given in Table V. Not all of them, however, are to be classified as varying, in spite of the three rhythms being present: nearly half (13 out of 28) fell into this group and there was little to say except that the different grades of heart block were present from time to time and one had not much idea what rhythm would be found at the next visit. These changes were of all types from Case 109 (p. 84) where the only cardiogram taken showed 2 : 1 block, dropped beats, and latent block in the three leads, or Case 112 who showed these three rhythms on the same day but generally had a slow heart (2 : 1 or complete block), to Case 107.

Case 107. A woman, aged 42, had rheumatic mitral disease without much evidence of stenosis. Her symptoms started with a Stokes-Adams attack and after many attacks she died in one in the

TABLE V
PATIENTS WITH LATENT HEART BLOCK AND HIGHER GRADES

| Case No. | Sex and Age D=Died n.t.=not traced | Aetiology | Wasser- mann reaction | P-R interval with | | Com- plete heart block | Stokes- Adams attacks | Bundle branch block |
|----------|--|-----------|--------------------------------------|-------------------|-----------------|---------------------------------|-----------------------------|---------------------------|
| | | | | latent block | 2 : 1 block | | | |
| 101 | m. 57 | D | Sy.; B.P. 250/130 (see p. 83) | + | 0.17 | 0.17 | + | — |
| 102 | m. 63-67 | D | Ath. aortic st. (see p. 81) | — | 0.22 | — | + | — |
| 103 | f. 66 | D | B.P. 250/115 (see p. 81) | — | 0.21* | 0.21 | + | — |
| 104 | m. 64-69 | | Heart + (W.R. +) | + | 0.34* | 0.31 | + | — |
| 105 | m. 67-75 | | Heart + (see p. 82) | — | 0.33 | 0.30 | + | St.A. |
| 106 | m. 64-65 | | Heart failure (see p. 82) | — | 0.20 | 0.19 | + | — |
| 107 | f. 42-47 | D | Rh. mitral st. (see p. 80) | — | {0.28* 0.32} | {0.24 0.36} | + | St.A. |
| 108 | m. 34-35 | D | Sy. (see p. 81) | (+) | 0.22 | 0.22 | + | St.A. |
| 109 | m. 52 | n.t. | Heart failure (see p. 84) | — | 0.17* | 0.19 | — | St.A. |
| 110 | f. 62-63 | D | Cor. atheroma | — | 0.24* | 0.24 | + | St.A. |
| 111 | m. 73-76 | D | Heart + (see p. 84) | — | 0.28 | — | + | St.A. |
| 112 | f. 72 | D | B.P. 200/100 | — | 0.29* | 0.28 | — | — |
| 113 | f. 29-43 | | Rh. aortic inc. (see p. 83) | — | 0.17* | 0.19 | + | — |
| 114 | m. 51 | n.t. | Heart + (see p. 81) | — | 0.21† | — | + | B.B.Bl.† |
| 115 | m. 66-67 | D | Heart failure (see p. 85) | — | 0.20 | 0.19 | — | St.A. |
| 116 | m. 66-67 | D | Heart + | — | 0.24 | 0.24 | — | St.A. |
| 117 | m. 56 | D | Heart + | — | —* | 0.26 | — | — |
| 118 | f. 61-64 | | Cor. ath. (see p. 81) | — | 0.24 | — | + | St.A. |
| 119 | m. 49-54 | | Cor. ath. (Sy.) | — | 0.44* | 0.44 | + | — |
| 120 | m. 58-60 | D | B.P. 210/130 (see p. 81) | + | 0.22 | — | + | St.A. |
| 121 | m. 68 | n.t. | Cor. ath.; B.P. 210/90 | — | 0.26 | 0.25 | — | St.A. |
| 122 | m. 74-78 | D | Heart + | — | 0.22 | — | + | St.A. |
| 123 | m. 46 | D | Sy. aortic incomp. (see p. 90) | — | 0.32 | 0.32 | + | St.A. |
| 124 | f. 65-67 | | B.P. 230/100 (see p. 81) | — | 0.28 | 0.29 | + | — |
| 125 | f. 58-68 | | B.P. 240/115 (see p. 82) | — | 0.23 | 0.42 | + | — |
| 126 | m. 43-48 | D | Ath. aortic st. and inc. (see p. 81) | — | 0.25 | 0.36 | + | St.A. |
| 127 | m. 61-62 | | Heart + (see p. 82) | — | 0.24 | 0.24 | + | St.A. |
| 58 | m. 76-79 | D | Heart + ; B.P. 280/100 | + | 0.36 | — | — | St.A. |

* Dropped beats also at other times.

† Nine years before.

fifth year. During this time she most often had 2 : 1 heart block, but sometimes 2 : 1 changing to latent, or latent block alone, and much less often dropped beats or complete heart block.

Adding these 13 to the 8 already classified as *varying* makes 21 in this group. The remaining 15 of the 28 will be discussed under the following headings though not all are finally accepted in these groups: progressive heart block (7 cases), remittent heart block (5 cases), and temporary heart block (3 cases: 1 transient and 2 paroxysmal).

Progressive heart block (7 cases). Here there was some evidence that the grade of block was progressive and finally became complete. On theoretical grounds this might be expected to be more common or almost the rule, but it does not appear to be so. Possibly it may occur more often as a short transient stage when the patient is not under observation, but beyond the cases to be quoted we have no evidence of this.

Only in 3 of the 7 was the first rhythm latent heart block.

Case 114. A P-R interval of 0.21 sec. with bundle branch block was recorded in 1929 in a man, aged 42; in 1938 he began to have attacks of giddiness for the first time and was found to have complete heart block, still with B.B.Bl.; nothing was known about his rhythm in the 9 years between.

Case 118. A woman, aged 60, who had had angina for 2 years and a stroke 5 years before, had a P-R interval of 0.23 sec.; a year later she was found to have complete heart block which persisted for the two years she was under observation; six weeks before this she had her first real Stokes-Adams attack so probably this was the time when her block became complete.

Case 120. A man, aged 58, with high blood pressure was observed regularly for a month with a P-R interval of 0.22 sec.; a year later he was seen with complete block and congestive failure from which he died eight months later; he had no Stokes-Adams attack till just before his death and there was no clinical evidence of when the change of rhythm took place.

Apart from the earlier observation of latent block these 3 might all be classed as established C.H.B. In the next two there was varying partial block as the first finding, and later one had varying and one established C.H.B. *Case 108* seems a good example of progressive heart block, but he started with Stokes-Adams attacks six months before his admission to hospital, so that probably he should be classed as varying becoming established. The last should certainly be classified as varying but was interesting from the progressive change in the P-R interval when there was a A-V conduction.

Case 103. In a woman, aged 66, with high blood pressure, dropped beats without progressive lengthening (P-R interval 0.21 sec.) were recorded when she was first seen and she died five months later, her rhythm during the last few months varying between 2 : 1 and complete block.

Case 124. In a woman, aged 65, with high blood pressure, partial block (dropped beats or sometimes 2 : 1 block) was always present during the first six months observation after which she always had complete block; her symptoms of dyspnoea and palpitation were much the same during the three years.

Case 108. A man, aged 34, always had a heart rate of about 66 and a P-R interval of 0.21 sec. for the first fourteen days in hospital. His heart rate then became slower and irregular (generally 40-48) and records showed latent and 2 : 1 block and a more deeply inverted T III. After six days his heart rate fell to 26-36 and apparently complete block became his usual rhythm after this. He was two more months in hospital and died suddenly eight months later.

Case 126. A man, aged 43, with aortic stenosis and incompetence of unproved ætiology, had complete heart block the first time he was seen, but the next time latent block and bundle branch block: and the figures in Table VI show that if the occasions with complete block were omitted there was a progressive lengthening of the P-R interval from 0.24 to 0.41 sec. during the course of three years. He died with congestive heart failure in the fourth year. There was no other case at all comparable with this.

Remittent complete heart block (C.H.B. interrupted generally by latent block (5 cases)).

Case 102. A man, aged 63, with atheroma and aortic stenosis was seen most months for three years and his heart rate was always between 30 and 44 (in cardiograms, C.H.B. with V. 36 to 44) except once during the first year when he had a heart rate of 76 with a P-R interval of 0.22 sec.

TABLE VI.—UNUSUAL PROGRESSIVE LENGTHENING OF P-R INTERVAL

| Date | | Rhythm | Bundle Branch Block | Heart rate | | P-R interval |
|-------------|----|-----------|---------------------|------------|-------|--------------|
| | | | | Aur. | Vent. | |
| 22/2/24 .. | .. | C.H.B. | B.B.Bl. | 100 | 48 | — |
| 9/5/24 .. | .. | Latent B. | N | 66 | 66 | 0.24 |
| 6/6/24 .. | .. | Latent B. | N | 50-60 | 50-60 | 0.26 |
| 10/10/24 .. | .. | 2 : 1 B. | N | 76 | 38 | 0.32 |
| 13/3/25 .. | .. | 2 : 1 B. | N | 86 | 43 | 0.32 |
| 5/6/25 .. | .. | 2 : 1 B. | N | 76 | 38 | 0.35 |
| 23/10/25 .. | .. | C.H.B. | B.B.Bl. | 86 | 39 | — |
| 12/2/26 .. | .. | 2 : 1 B. | N | 80 | 40 | 0.41 |
| 11/3/27 .. | .. | C.H.B. | B.B.Bl. | 110 | 55 | — |
| 27/9/27 .. | .. | (C.H.B.) | B.B.Bl. | 76-81 | 38 | (0.48)* |
| 15/6/28 .. | .. | C.H.B. | B.B.Bl. | 62 | 42 | — |

* Some of this was certainly C.H.B.: some looked like 2 : 1 block with a P-R interval of 0.48 sec., but it might have been chance with the auricular almost exactly twice the ventricular rate.

Case 125. This woman of 58 with high blood pressure was seen regularly for eleven years and always had complete block at each visit, except once in the sixth year when she was seen with normal rhythm at a rate of 60 (to 78) with a P-R interval of 0.23 sec. (Fig. 8), and once in the seventh year when she had a record of 2 : 1 and 3 : 1 block (P-R, 0.40 and 0.26 sec. respectively).

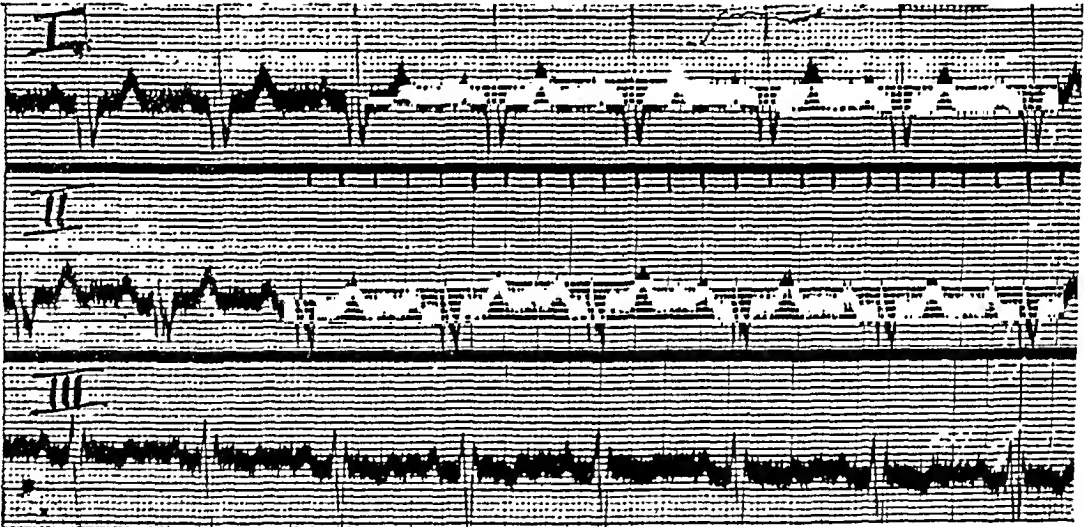


FIG. 8.—Sinus rhythm with latent block, P-R 0.23 sec., interrupting complete heart block that had been established for six years (Case 125).

Case 106. This man of 64 attended regularly for a year and always had complete block except once when latent and 2 : 1 block were both observed.

Case 127. This man of 61 was seen regularly for about 18 months and generally had 2 : 1 or complete block, but on two occasions his heart rate changed from about 40-44 to 60-78 when he had normal rhythm with a P-R interval of 0.24 sec.

Case 105. The last case was less striking, and might have been included on varying. A man, aged 64, always had complete heart block when in hospital in 1931. In 1934, when followed up, he was seen with 2 : 1 block (rate 32; P-R 0.30 sec.) and with latent block (rate 52; P-R 0.33 sec.). In 1939, when he was in hospital again with carcinoma of the penis, he had complete block.

Dividing up the progressive group, where the cases could generally be classified in one of the larger groups, and omitting those where the period of observation was only short, the distribution was as follows:

| | |
|---|----------|
| Established heart block | 18 cases |
| Remittent heart block | 5 cases |
| Varying, latent, or partial, becoming established | 7 cases |
| Varying heart block | 23 cases |
| Paroxysmal and transient block | 3 cases |

PAROXYSMAL HEART BLOCK

Before discussing paroxysmal heart block, previous papers on the subject will be considered very shortly. After the case of Hay (1906) with 2 : 1 heart block and a normal a-c interval, Gossage (1909) described a case with intermittent complete block and a normal P-R interval at other times. In the well-known case of Starling (1921) Stokes-Adams attacks could be induced by swallowing though the P-R intervals were normal, but later complete heart blocks became established. Carter and Dieuaide (1923) collected 8 such cases and added one of theirs where there were repetitive Stokes-Adams attacks with complete block just after, and a normal conduction time between the attacks: they called it recurrent or intermittent heart block.

Comeau (1937) accepted 12 of 20 possible reported cases as proved examples of paroxysmal heart block and added 1 of his own; most had Stokes-Adams attacks but it was not an essential feature. The same year Gilchrist (1937) said he had seen 8 cases where the sequence of events was normal rhythm, Stoke-Adams attack, complete heart block (for minutes or hours), and then again normal rhythm with a normal P-R interval; he gave details of 2 of the cases, one proved electrocardiographically, and the other by a heart rate of 35 and improvement with ephedrine. Paul White (1937) speaks of cases of heart block as temporary and functional or permanent and organic, but this does not seem to be a sufficient division. Other cases have been mentioned in the paper of Laurence and Forbes (1944). The terms paroxysmal, intermittent, and recurrent have been used indiscriminately for this condition. The former seems the most suitable term for this clinical picture, partly because it is already used for paroxysmal tachycardia and paroxysmal auricular fibrillation.

It has generally been limited to cases where the P-R interval was normal in between, but this prevents such a diagnosis being made precisely in many cases when no graphic record can be obtained of the usual rhythm with a normal heart rate. I suggest that paroxysmal heart block should be used as a clinical term when a normal heart rate with or without latent block is the usual rhythm and heart block the occasional finding. The two groups could be distinguished as paroxysmal heart block (complete) when the P-R interval is normal in the interval, and paroxysmal complete heart block, when there is latent block in the interval. This distinction is of practical importance, for the diagnosis of some Stokes-Adams attacks will be missed unless the existence of paroxysmal heart block (complete) is more widely recognized, because the normal P-R interval found in between will lead to the false assumption that the syncopal or epileptiform attack can not have been of the Stokes-Adams type. Dr. Suzman's case at the end of the appendix is a good illustration of this difficulty.

The term transient heart block could be used when there is a known temporary cause, such as infection or immediately after cardiac infarction.

Transient heart block. One patient fell into this group, as she had temporary block due to an acute infection.

Case 113. A woman, aged 28, already had aortic incompetence and in her third attack of rheumatic fever developed complete block which lasted for a week and was followed by partial block, sometimes with dropped beats and sometimes 2 : 1, this persisting for three months. Full details have been published (Campbell, 1931). In spite of this she made an excellent recovery and is still in good health 14 years later with a normal P-R interval. In this time there has been very little change, and she is able to do a fair amount of work running her father's house.

Paroxysmal heart block. Two patients were included in this group without any doubt.

Case 101. A man, aged 57, with a blood pressure of 250/130 was in hospital with symptoms suggestive of neuro-syphilis and a stroke four years before. He was found with complete heart block which changed sometimes to 2 : 1 and sometimes to occasional ventricular responses with a P-R interval of 0.17 sec. After two weeks the block disappeared and for the rest of the time in hospital he had normal rhythm with the same length of P-R interval. He had a large heart, a strongly positive Wassermann reaction, and mental symptoms suggestive of general paralysis, and unfortunately he was lost sight of as it was necessary for him to be transferred to a mental hospital.

Case 111. A man, aged 73, with high blood pressure, was admitted with Stokes-Adams attacks. He was found to have complete heart block which persisted for four weeks. It then changed to sinus rhythm with bundle branch block and a P-R interval of 0.27 sec., and this persisted for the next month in hospital, and was still present when he was seen a year later. Such an occurrence is, of course, not uncommon where complete block occurs temporarily after a coronary thrombosis, but there was no evidence of this in his case.

With the classification proposed this would be paroxysmal complete heart block, as latent block was present when he had sinus rhythm, and Case 101 and Dr. Suzman's case in the appendix would be paroxysmal heart block (complete).

There are four other cases that must be considered shortly here as they all had heart block (3 with complete and 1 with 2:1 heart block) and at other times sinus rhythm with a P-R interval that was nearly or quite normal.

Case 106 (p. 82) has been described as remittent because complete block was always found except once when he had 2:1 block (P-R, 0.19 sec.) and latent block (P-R, 0.20 sec.).

Case 115. This man, aged 66, was included as varying heart block because there were frequent proved changes of 2:1 (P-R, 0.19) and latent block (P-R, 0.20 sec.) and presumed complete block as he started with a Stokes-Adams attack and had several others.

Case 109. This man, of 52, was also included as varying, since 2:1 and dropped beats and latent block with a P-R interval of 0.17 sec. were all observed in quick succession: his after history is unfortunately not known and his heart failure may have been due to an acute infection or to infective endocarditis.

Finally Case 103 was included as progressive (partial to varying), but if a P-R interval of 0.21 sec. in an elderly woman may be regarded as normal she could also be regarded as paroxysmal heart block in the sense in which this has generally been used. These last two patients were included by Laurence (1944) being quoted from Table III of an earlier paper (Campbell, 1943b).

2:1 HEART BLOCK

This is a much less stable rhythm than complete heart block. It must be very rare for it to persist without changes for long periods, though in a few patients it seems the dominant rhythm for some time, occasionally even for years. There were 4 cases with 2:1 and complete heart block. In 2 of these frequent changes were observed during the 2 and 5 years respectively that they lived. In the third the block was always, I think, 2:1 during the month he was in hospital except once when the rare 3:1 rhythm was observed, probably due to atropine. Soon after it became complete and so far as I know this continued for the remaining 12 years of his life, except once in the second year when 2:1 block was again recorded (Case 142, see appendix). The fourth has been traced recently after six years (Case 143).

Case 143. A man, aged 38, became short of breath rather suddenly and had at first some minor Stokes-Adams attacks. When seen recently and at the first visit 2:1, 3:1, and complete block were all recorded: he was quite familiar with the change, which took place frequently, but it seemed that 2:1 had remained his predominant rhythm during all the period and that the other rhythms were only present for a short part of the time.

Of the 3 cases where only 2:1 block was recorded, none had cardiograms frequently, but in 2 this rhythm seemed persistent and in 1 a heart rate of 70 was observed clinically during the four to six weeks in hospital.

There were also 7 cases where 2:1 and latent block were the only rhythms recorded, but in at least 3 of these there was good clinical evidence of complete block and as 5 of the 7 had Stokes-Adams attacks it was probably present in more than this.

3:1 heart block. This is a much less common rhythm and I have never seen it persist. It is seen most often as a change from 2:1 heart block as in Fig. 9.

The P-R interval in 2:1 heart block. This should have been dealt with in the paper on partial heart block (Campbell, 1943b), but was only referred to incidentally when patients had this rhythm and dropped beats as well. It was generally of about the same length as the

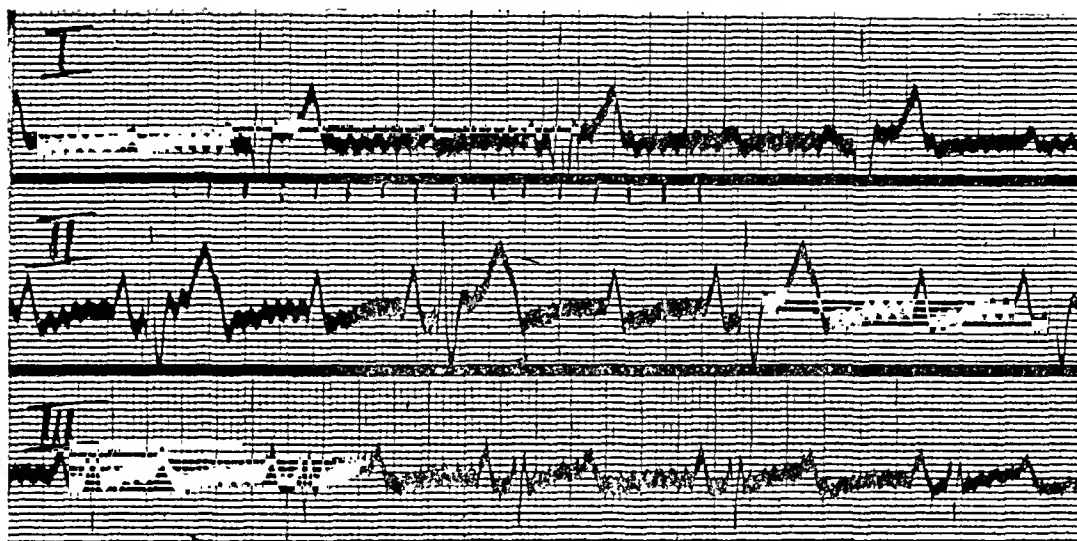


FIG. 9.—3 : 1 heart block in a man who at that time generally had 2 : 1 heart block (as in lead III) and for twelve years afterwards had complete heart block (Case 142). There was little if any change in the P-R interval, which was about 0.21 sec.

first P-R interval with a response. There were 29 cases with records of 2 : 1 block and the P-R intervals were as follows:

Less than 0.20 secs., 8 cases; 0.21–0.22 sec., 4 cases; 0.23–0.24 sec., 5 cases; 0.25–0.26 sec., 2 cases; 0.27–0.32 sec., 7 cases; 0.36, 0.40, and 0.42 sec., 3 cases.

I was surprised that in nearly one third of the cases the P-R interval was normal and sometimes as short as 0.16 sec. In 3 of the 7 cases where 2 : 1 block was the only rhythm observed the P-R interval was normal and only in 2 of the 7 was it over 0.24 sec. The average for all the cases was 0.254 sec. This is identical with figure found for the P-R interval with latent block in cases that had 2 : 1 or complete block also (Campbell, 1943c, Table IV). The spread was rather wider as shown by the quantities, 0.19 and 0.30 sec. against 0.215 and 0.270 sec. The fact that the increase in the P-R interval is small or absent in so many cases of 2 : 1 heart block shows again that a defect of excitability or some other factor as well as a defect of conductivity is needed to explain the observed facts.

PROGNOSIS

Two thirds of the cases have died and one third were still alive when last seen after an average period of 6 years. Of the 64 cases, 14 were under observation for a short period only, so have been omitted, leaving 50 for consideration. Of these, 34 died, 10 in less than a year, 9 in the second year, 14 in from 2–6 years, and 1 (Case 142, appendix) after 12 years. The average period of survival was 2.5 years.

Of the 16 who were still alive, 2 were under observation for more than one but less than two years, 8 for from 2–6 years, and 6 for 7, 7, 8, 11, 14, and 20 years respectively. The average period of survival was 6 years. Possibly the last two (Cases 113 and 140, see appendix) should be omitted as the first had transient block during acute rheumatism and the second may have had congenital block though this was not the diagnosis made at the time: if so, the average period would be reduced to 4.4 years. These results are shown in Table VII.

TABLE VII

| | | LENGTH OF LIFE AFTER OBSERVATION OF HEART BLOCK | | | | | | | | |
|-------------------------------|----|---|---------------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------------|
| Length of period | .. | .. | Less than 1 year | 1-2 years | 2-3 years | 3-4 years | 4-5 years | 5-6 years | 6-9 years | 10 years or more |
| No. of patients who have died | | | 10 | 9 | 3 | 4 | 3 | 4 | 0 | 1 |
| No. of patients who are alive | | | 0 | 2 | 3 | 3 | 1 | 1 | 3 | 3 |

The figures agree surprisingly closely with those of Graybiel and White (1936), which suggests that the series are large enough to give an accurate picture. They found that 49 patients had died after an average period of under 3 years, and that 17 were alive after an average period of just under 7 years.

As a contrast the average duration of life in my 10 congenital cases is 22 years, and 7 of the 10 are known to be still living.

From such figures one can calculate the expectation of life if one assumes that surviving patients continue to die at the same rate as those who have died already—probably a pessimistic assumption. If x per cent are alive after an average period of b years, and $100-x$ per cent have died after an average period of a years, $100-x^2/100$ will have died after $2a$ years and $\frac{100a-ax+(x-x^2/100)(a+b)}{100-x^2/100}$ will be an approximation to the average duration of life for all cases.

This gives 4.6 years as the expectation of life for complete heart block calculated from my figures and 4.5 years from those of Paul White and Graybiel (1936). The prognosis is better than that for bundle branch block, 3 years, but worse than that for a recent cardiac infarct (excluding deaths in the first six weeks) where it was 6.5 years, these figures having been calculated in the same way from my own cases.

Changes of rhythm did not seem to affect the prognosis unless these were associated with Stokes-Adams attacks. Thus there was no difference as regards prognosis between those having complete heart block *with* latent block and those having complete heart block *without* latent block. If Stokes-Adams attacks are more frequent with changes in the degree of block, a worse prognosis might have been expected. The apparent anomaly might be because there were some cases without proved latent block who had nevertheless changes of rhythm of other types or changes observed clinically but not recorded. The 11 cases of this type were, therefore, transferred and the two groups were analysed again as regards prognosis. But there was still no great difference (see later).

Undoubtedly the prognosis was specially bad in the group with frequent changes of rhythm and Stokes-Adams attacks when they were first seen, but this happened to be balanced by the man who lived 12 years with Stokes-Adams attacks, although at first he had frequent changes of rhythm, and by other similar cases.

There were 36 cases having heart block *without* latent block; 25 of these were under observation for a reasonably long period. Eighteen of these died and 7 were still alive when last heard of. Ten died in less than 2 years; 7 in from 2-6 years; and 1 after 12 years; the average period of survival being 2.7 years. Of the 7 who were still alive, 4 were under observation for from 2-6 years, and 3 for 7, 7, and 20 years respectively; the average period was 4.5 years or 7 years if the last exceptional case was included.

There were 28 cases having heart block *with* latent block; 25 of these were under observation for a reasonably long period. Sixteen of these died and 9 were still alive when last heard of. Nine died in less than 2 years and 7 in from 2-6 years, the average period of survival being 2.3 years; this was a little shorter than in the group without latent block but the difference was not significant. Of the 9 who were still alive, 2 were under observation for more than 1 year, 4 for from 2-6 years, and 3 for 8, 11, and 14 years respectively; the average period was just over 6 years, or 4.3 years if the last case be excluded. Again the period was a little shorter but the difference was not significant.

If the patients were divided into two groups—those known to have different grades of heart block and those only known to have complete block—by the transfer of the 11 cases referred to, the difference between the two groups were still slight.

There were 25 cases *without change of rhythm*, 8 of whom were not traced: 11 died (5 in less than 2 years, and 6 in from 2-6 years), the average period of survival being 2.5 years; and 6 were still alive (4 after 2-6 years, 1 after 7 years, and 1 after 20 years), the average period being 7.0 years, or 4.3 years if the last case be excluded.

There were 39 cases *with change of rhythm*, 6 of whom were not traced: 23 died (14 in less than 2 years, 8 in 2-6 years, and 1 in 12 years), the average period of survival being 2.7 years (2.3 years without the last case); 10 were still alive (2 after 1 year, 4 after 2-6 years, and 4 after 7, 8, 11, and 14 years), the average period being 4.4 years, or 5.4 years if the last case be excluded.

Incidence of Stokes-Adams Attacks

Just over half the patients with complete and/or 2 : 1 heart block had Stokes-Adams attacks—33 out of 64. Originally, as the relationship with latent block was being specially investigated, they were divided into two groups—those with and those without recorded latent block—and rather surprisingly in view of the reputed association of Stokes-Adams attacks with a changing degree of block there was no significant difference in the incidence of Stokes-Adams attacks (53 against 50 per cent). But there is no great danger in the change from latent block to dropped beats or to 2 : 1 block when no new centre has to take control, and it is only the change from one or other of these rhythms to idiopathic ventricular rhythm that is attended by the risk of a Stokes-Adams attack.

Among the group without recorded latent block there were 4 with 2 : 1 block, and 7 with faster rates that did not chance to be graphically recorded. Here the incidence of Stokes-Adams attacks were specially high, 10 of these 11 cases, possibly because they were in hospital for their Stokes-Adams attacks just at a time when these were most frequent owing to the frequent changes of rhythm. If these 11 cases were moved, 25 of the 39 with known change of rhythm had Stokes-Adams attacks (64 per cent), and only 8 of the 25 with no known change from their complete heart block (32 per cent). This is not meant to imply that even in these last there was not a change of rhythm at the time of their Stokes-Adams attacks, but that no such changes were noted at other times when they were under observation, and that the precise behaviour of the heart with their attacks was not known. There were several cases where Stokes-Adams attacks were more frequent at or near the start and the patient "grew out" of them. This may be partly due to the habituation to the slow ventricular rate and to the ventricle having become accustomed to its responsibility for initiating and maintaining the heart beat. For example, Case 136 had two Stokes-Adams attacks when 66; when 68 he was in hospital and though during the first two weeks his heart rate varied between 40 and 72 he had no more than attacks of faintness; there was little change when he was 70 and he had had no real Stokes-Adams attacks since the first two. Case 143 (p. 84) gave a very similar history. Case 145 had frequent attacks all through the day for ten days at the start when he was 62; he lived 6 years after this and the attacks were not very frequent though they continued. In Case 147 the first attack was the only typical one, though he had attacks of faintness when things went black for the remaining nine months of his life.

Prognosis with Stokes-Adams Attacks

As some of the cases were not traced there were 50 available for assessing the prognosis. It was considerably worse when there were Stokes-Adams attacks, 80 per cent of these patients having died against 50 per cent of those without such attacks.

TABLE VIII

STOKES-ADAMS ATTACKS AND PROGNOSIS

| | Total | Alive when last heard of | Dead | Not traced |
|--------------------------------------|-------|--------------------------|------|------------|
| Patients with Stoke-Adams attacks | 33 | 6 | 24 | 3 |
| Patients without Stoke-Adams attacks | 31 | 10 | 10 | 11 |

Unfortunately there were far more who were not traced among the patients without such attacks, and if all these were included the percentage figures were:

| | | | |
|------------------------------|----|----|--|
| With Stokes-Adams attacks | .. | .. | Known to be alive, 19 per cent; dead, 73 per cent. |
| Without Stokes-Adams attacks | .. | .. | Known to be alive, 33 per cent; dead, 33 per cent. |

Although more of the patients had died while under observation the length of time before death was not significantly different, the average for both groups being between 2 and 2.5 years. This apparent anomaly is explained by the fact that there are more of the patients without Stokes-Adams attacks still surviving, who will later increase the average duration of life considerably.

There was no noticeable difference in any of these findings between the patients who had and those who had not latent heart block. All the figures have therefore been combined.

Method of dying. The great danger of sudden death in patients with Stokes-Adams attacks has of course been emphasized for a long time. This was again confirmed in the present series, but I was surprised to find that there was only one record of sudden death in the patients with complete heart block where a history of Stokes-Adams attacks had not been noted. No doubt patients with or without previous heart block may sometimes die in their first Stokes-Adams attacks and so come under the notice of the pathologist rather than of the clinician, but in this series only one patient seen with heart block without any evidence of Stokes-Adams attacks is known to have died suddenly. There were a few without Stokes-Adams attacks when first seen who developed this later and so lost their immunity from sudden death, but even so the point seems of considerable value for prognosis.

Of the 24 patients with Stokes-Adams attacks who died, no less than 14 died suddenly (almost certainly in attacks), 3 died with heart failure, and in 7 the method of death was not known.

Of the 10 patients without Stokes-Adams attacks known to be dead, 1 died suddenly, 3 had congestive heart failure, 1 left ventricular failure, 1 broncho-pneumonia, 1 cerebral hæmorrhage, 1 intestinal obstruction, and in 2 the method of death was not known.

One practical and valuable conclusion from these facts is that the patient who has not had a Stokes-Adams attack in the first month or so of his heart block is not very likely to develop such attacks, and the longer the time that passes without them, the more certain one can be that there is small risk of his dying suddenly.

SUMMARY AND CONCLUSIONS

Complete heart block is most often seen in men in the seventh decade with enlarged hearts and atherosclerosis but no other evidence of gross heart disease. Four-fifths of our patients were men. Most (45 per cent) were between 60 and 69, and 84 per cent were over 50 years of age at the onset of complete block.

Syphilitic and rheumatic heart disease were between them responsible for only just over 10 per cent of the cases. Other myocardial disease was responsible in 75 per cent, or in 86 per cent if the group of congenital cases was excluded, this being the second commonest cause (13 per cent). Cardiac enlargement with no other signs than atherosclerosis of the aorta and often of peripheral arteries was the evidence of myocardial disease in nearly half these cases, high blood pressure, angina pectoris, or congestive failure being present in the other half. In the 10 cases with high blood pressure the average figure was 225/108. In the others the systolic pressure was above and below 160 in equal numbers and the average figures for these two groups were 194/81 and 137/73. Thus, in the latter the pulse pressure was only slightly raised, but in the former and in those with high blood pressure, the pulse pressure averaged 115. The reasons for this have been discussed.

The heart rate was usually between 28 and 40 and averaged just under 35 (excluding congenital cases where it was generally 40-56).

Heart block may be of very varied types: it may be (1) complete; (2) partial; 2 : 1, or more rarely 3 : 1 or 4 : 1; (3) partial with dropped beats only; including regular 4 : 3, 3 : 2, etc. or occasional dropped beats; or (4) latent, with a prolonged P-R interval only.

In addition to this there may be various changes and combinations which can be usefully described as follows. Complete heart block may be *established*, or *varying*, changing to other degrees of block, or *interrupted*. It may also be *transient*, due to a known infection or to a specific episode such as cardiac infarction, or *paroxysmal*, of which there are two varieties, *paroxysmal complete heart block* when the usual rhythm is latent heart block, and *paroxysmal heart block (complete)*, when the usual rhythm shows a normal P-R interval. These varieties and combinations have been discussed.

Prognosis. Complete heart block is a serious lesion, though some patients, especially some of those under 40, live for many years in reasonably good health. There were 50 cases followed for more than 2 years or until their death; 34 were dead after an average period of 2.5 years; 16 were alive after an average period of 6 years or 4.5 years if two exceptional cases were excluded. Of the former, 19 died in less than 2 years, 14 in from 2–6 years, and 1 after 12 years. Of the latter, the period of observation was from 2–6 years in 10, and from 7–20 years in the other 6 cases.

Stokes-Adams attacks. These were present in half the patients with complete heart block. When they were present they were one of the earliest if not the first significant symptom of heart block in three-quarters of the cases. In those without Stokes-Adams attacks, dyspnoea or attacks of faintness or dizziness were the main presenting symptoms.

Stokes-Adams attacks were no more common in those who had *recorded* latent heart block than in those without. A known change of rhythm at times other than those of the attack does make Stokes-Adams more likely but not as much as might be expected (64 against 32 per cent).

The prognosis was considerably worse in those with Stokes-Adams attacks, the results in the patients traced being:

| | | Alive | Dead |
|------------------------------|-------|-------|------|
| With Stokes-Adams attacks | | 6 | 24 |
| Without Stokes-Adams attacks | | 10 | 10 |

The method of dying was even more strikingly different: of the patients with Stokes-Adams attacks, 61 per cent died suddenly, presumably in attacks; of those without Stokes-Adams attacks, only one was known to have died suddenly and 50 per cent died with failure. If when a patient is first seen with complete heart block he has not had a Stokes-Adams attack, the risk of such an attack developing or of his dying suddenly is not great, and with each month that has passed the risk becomes still less.

It is important to realize that Stokes-Adams attacks may occur with paroxysmal heart blocks (complete) and the paroxysms may be of short duration after the attacks and may easily be missed. Otherwise attacks that are true Stokes-Adams attacks will remain unexplained.

I should like to express my thanks again to my colleagues at Guy's Hospital and at the National Hospital for Diseases of the Heart, and especially to Dr. S. Suzman, my clinical assistant, and Mr. F. H. Muir, technician to the Cardiographic Dept., Guy's Hospital, for helping me to keep in touch with so many of these patients.

REFERENCES

- Campbell, M. (1931). *Lancet*, 2, 180.
 — (1943, a). *Brit. Heart J.*, 5, 15.
 — (1943, b). *Ibid.*, 5, 55.
 — (1943, c). *Ibid.*, 5, 163.
 Carter, E. P., and Dieuaide, F. R. (1923). *John Hopkins Hosp. Bull.*, 34, 401.
 Comeau, W. J. (1937). *Amer. J. med. Sci.*, 194, 43.
 Duras, P. F. (1944). *Brit. Heart J.*, 6, ..
 Gilchrist, A. R. (1937). *Brit. med. J.*, 1, 203.
 Gossage, A. M. (1909). *Heart*, 1, 283.
 Graybiel, A., and White, P. D. (1936). *Amer. J. med. Sci.*, 192, 334.
 Hay, J. (1906). *Lancet*, 1, 139.
 Lawrence, J. S., and Forbes, G. W. (1944). *Brit. Heart J.*, 6,
 Parkinson, J., Papp, C., and Evans, W. (1941). *Ibid.*, 3, 171.
 Starling, H. J. (1921). *Heart*, 8, 31.
 Stern, V. S. (1944). *Brit. Heart J.*, 6, 66.
 White, P. D. (1937). *Heart Disease*, 2nd ed., p. 673.

An Unusual Case of Stokes-Adams Attacks and Paroxysmal Heart Block

Case 123. K. R. had malaria, dysentery, and gonorrhœa in Rhodesia; the last was treated very inadequately and was followed by crippling arthritis. Soon after he began to have attacks of vomiting with blood in the vomit and 7 years later, as this persisted, Sir Arthur Hurst diagnosed gastritis polyposa and arranged for gastrectomy (*Hurst, A. F., and Stokes, A. (1926), Guy's Hosp. Rept., 76, 351*). So far no mention has been made of his heart but section of some of the larger vessels of the stomach showed arteriosclerotic changes.

In 1923, when he was 34, he had his first syncopal attack and only remembered finding himself on the ground surrounded by servants. In 1927-8 he had 2 or 3 more attacks and in 1929 when on leave had 4 attacks in four months. Nearly all occurred when he was standing and drinking whisky. They were preceded by a momentary feeling of nausea and sometimes, if he was sitting, he had this feeling without any after developments. He never hurt himself in falling and thought he was out for up to a minute. Afterwards he felt unsteady and sometimes vomited a little bile but recovered quickly and could take another drink without effect.

In 1929-34 he had 7 or 8 more attacks. In 1935 he was readmitted to Guy's Hospital for severe arthritis of his spine and large joints. His heart rate was slow, due to varying heart block, most often 2 : 1, sometimes complete or latent. The heart was just enlarged and there was an aortic diastolic murmur. The W.R. was negative. He had no more attacks in hospital but died six months later.

Here, no precise diagnosis of the cause of the syncopal attacks were possible until some years later he developed varying heart block: it is still only a reasonable deduction that they were Stokes-Adams attacks and that he had paroxysmal heart block; it seems that drinking spirits may have been a special provoking cause as swallowing was in the case of Starling (1921).

C.H.B. of Doubtful Actiology: Good Health after 20 Years

Case 140. K. H. had her first and only attack of fainting when she was 19, and C.H.B. was diagnosed then. She was seen by me 12 years later, complaining of no more than some breathlessness and giddiness, and she remained under regular observation for 8 years more.

Her heart was considerably enlarged to the left with an apical systolic murmur; her B.P. remained about 180-200/80-90; her W.R. was negative; and there was no evidence of valvular disease. Her heart rate was early always between 30 and 40 and the only other cardiographic abnormality was left ventricular preponderance which remained unchanged. She continued in good health able to do light house work. It has not been possible to trace her as the area where she was last living has been bombed.

She was classified as a rheumatic case because of a history of doubtful rheumatic fever when she was 10 but there was no clinical or radiological evidence of mitral stenosis. On reviewing her case I feel it much more probable that this was a case of congenital heart block that I failed to recognize, even in my recent paper (Campbell, 1943, a).

Unusual Length of Life with Stokes-Adams Attacks

Case 142. J. H., a seaman, had no history of rheumatic fever or syphilis, and his W.R. was negative. He always had good health and served in the war 1914-18 without any complaints. In 1919, when 43, he began having attacks in which he went unconscious and fell. At first they were preceded by precordial pain which spread up the left side to the angle of the jaw and this seems to have been most severe with the first attack. His only other symptom was dyspnoea, but he had to give up work because of the frequency of the attacks—at least one a month.

In 1927 Dr. L. Forman wrote to me as follows: "This man was admitted to hospital as an epileptic. During an observed attack he became very pale and his pulse could not be obtained; later it became regular at 20 a minute; and has since been about 45." He was admitted under my care and was found to have 2 : 1 heart block (V, 40-48). His heart was slightly enlarged and his arteries extremely thickened. During a month in hospital he had no attacks. All records showed 2 : 1 block, even when his auricle was quickened to 120 with exercise, except once when he had been given I.A.H. 1/150 grain 4 hourly, enough to produce dryness of the mouth; he then showed 3 : 1 heart block (Fig. 9). Records of his B.P. varied, e.g. 160/90, 180/90, 170/110. A year later he came up with a pulse of 32 due to C.H.B.; his B.P. was 230/120. With these two exceptions there was no change in his condition. The following months he again had 2 : 1 block after which every record for the next 10 years showed complete block.

He was last seen in 1938 and had been frequently an out-patient and three times in hospital. His attacks had continued unchanged though no others were observed. His description of the attacks was very much the same as at the start, but the pain became a more permanent feature again: it has an even more typical anginal spread but he had no regular angina of effort. In his later years the B.P. was generally about 240/90. In some of his more severe attacks he bit his tongue and passed water—episodes which are stated not to occur in Stokes-Adams attacks, but it seems unlikely that this was a case of complete heart block developing in an epileptic and I have a direct observation by a competent observer confirming the absence of the pulse during an attack.

He died suddenly in his sleep in 1939, 20 years after the first attack and 12 years after he came under observation with heart block.

C.H.B. of Unknown Actiology with Relatively Fast Ventricular Rate

Case 159. W. W. complained of nothing till she had three or four fainting attacks when she was 18. Her doctor told her her heart was slow and sent her to hospital when complete heart block with a rate of 40-48 was confirmed. Her heart was a little enlarged with a systolic murmur; nothing else abnormal was found; B.P. 135/70. Her slight dyspnoea improved with symptomatic treatment; her fainting attacks did not recur, and she was working and leading a normal life six years later.

The diagnosis of congenital C.H.B. was excluded because when she had scarlet fever at the age of 11, the three recorded pulse rates were 100, 70, and 90, and there had been no comment on her heart then or when she had pneumonia as a child. She had no family or personal history of rheumatic fever and I did not think she had mitral stenosis though this was difficult to exclude with absolute certainty; nor had she any history of diphtheria. Although she had no signs of congenital syphilis and a negative W.R. she was classified as syphilitic because her father had died of general paralysis, but I feel less certain now that she was not a case of congenital complete heart block.

The effect of exercise was carefully observed on several occasions and she was unusual in that the ventricular rate could be increased to 70 (Fig. 10). The A/V ratio varied on different days but tended to be fairly constant during and after exercise on a particular day (see Table IX, where some rates recorded graphically are given). This relative constancy of the A/V ratio suggests that both were being influenced by the same factor, possibly by the carbon dioxide content of the blood.

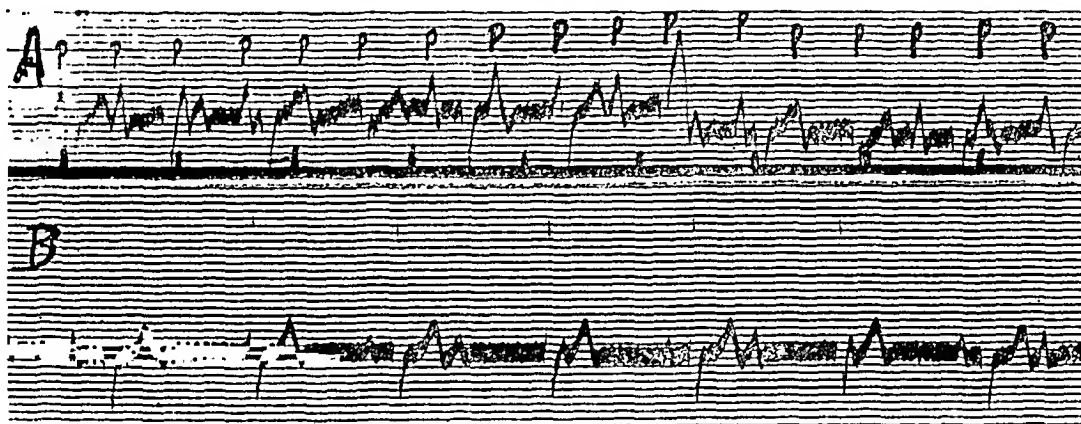


FIG. 10.—Complete heart block of unknown actiology (? congenital syphilitic) with a relatively rapid rate of 48 at rest (B) and a faster rate of 70 after exercise (A) from Case 159. In (A), which is lead I, the P waves have been marked; (B) is lead II. The time marker in (A) has been inked in to indicate seconds.

TABLE IX

AURICULAR AND VENTRICULAR RATE AT REST AND AFTER EXERCISE

| Date | Auricle | Ventricle | Ratio |
|-----------------------|---------|-----------|-------|
| <i>At rest</i> | | | |
| 27/5/27 | 77 | 49 | 1.57 |
| 21/7/27 | 74 | 42 | 1.78 |
| 25/1/28 | 79 | 44 | 1.79 |
| 24/5/28 | 75 | 48 | 1.56 |
| <i>After exercise</i> | | | |
| 27/5/27 | 112 | 70 | 1.60 |
| | 78 | 50 | 1.56 |
| 21/7/27 | 106 | 59 | 1.80 |
| " | 87 | 48 | 1.80 |
| " | 76 | 44 | 1.72 |
| 25/1/28 | 111 | 60 | 1.85 |
| | 102 | 50 | 2.04 |
| 24/5/28 | 110 | 71 | 1.55 |
| " | 86 | 56 | 1.54 |
| " | 75 | 48 | 1.56 |

Dr. Suzman's Case. Stokes-Adams Attacks with Paroxysmal Heart Block (Complete)

The following patient, notes and records of whom have kindly been lent me by Dr. S. Suzman, had Stokes-Adams attacks due to ventricular standstill without any evidence of heart block except

for a few minutes after a recorded Stokes-Adams attack. She did have bundle branch block but this was not persistent.

In 1937, when she was 64, she had her first attack of gall-stone colic and jaundice. In April 1941 she noticed she was short of breath and in August she became giddy and collapsed. In September, after another collapse, she was admitted to Guy's Hospital and diagnosed by Dr. Suzman as having Stokes-Adams attacks; she had bundle branch block (B.B.Bl.) with a P-R interval of 0.17 sec. Attacks were frequent enough for Dr. Suzman to hope for a graphic record, and after waiting some hours with everything ready he succeeded.

Before the attack there was B.B.Bl. with a normal P-R interval; in the attack there was ventricular standstill for nearly 30 seconds; and after the attack there was probably complete heart block lasting for at least a minute. At this stage no further film was available and the next day there was again B.B.Bl. with a P-R interval of 0.17 sec. She was discharged soon after and during the next month cardiograms taken while she was an out-patient were normal in every way except for rather low T waves, the P-R interval being 0.16 sec.

In January 1942 she was admitted to another hospital, and in view of her recurrent attacks of colic it was decided to remove the gall bladder, and this was followed by a second operation three weeks later for localized peritonitis. She was home well in April. During this stormy period her heart rate was regular and 70-90 a minute, except for some days after her operation, when it rose to 120, and no attention would have been drawn to her heart apart from the recent history of the attacks, which did not recur. Throughout her stay she took ephedrin, 1/2 grain daily. Her heart was enlarged (16.5 cm. m.t.d. in a chest of 26 cm.). The B.P. was 110/70.

A RARE CASE OF COMPLETE HEART BLOCK

BY

KEMAL SARACOGLU

From the International Clinic, Constantinople

Received October 23, 1943.

Complete heart block is not rare, but the case to be described has some very unusual features. A woman, aged 50 years, working as a doctor's servant, first came to us in March, 1937, for intestinal worms. She also complained of anxiety and dyspnœa, but at the first consultation nothing was mentioned about her real illness.

On 23/2/38 she came again for her heart disease. She complained of anxiety, heartache, and dyspnœa. Her illness had begun three months before and she stated that she suffered more during the night than the day. She was married and had borne five children, who had all died during the first days of their life. Her husband had died after a short illness, but she did not know the name of his disease.

At the examination of the patient we observed the following: her face was pale and her

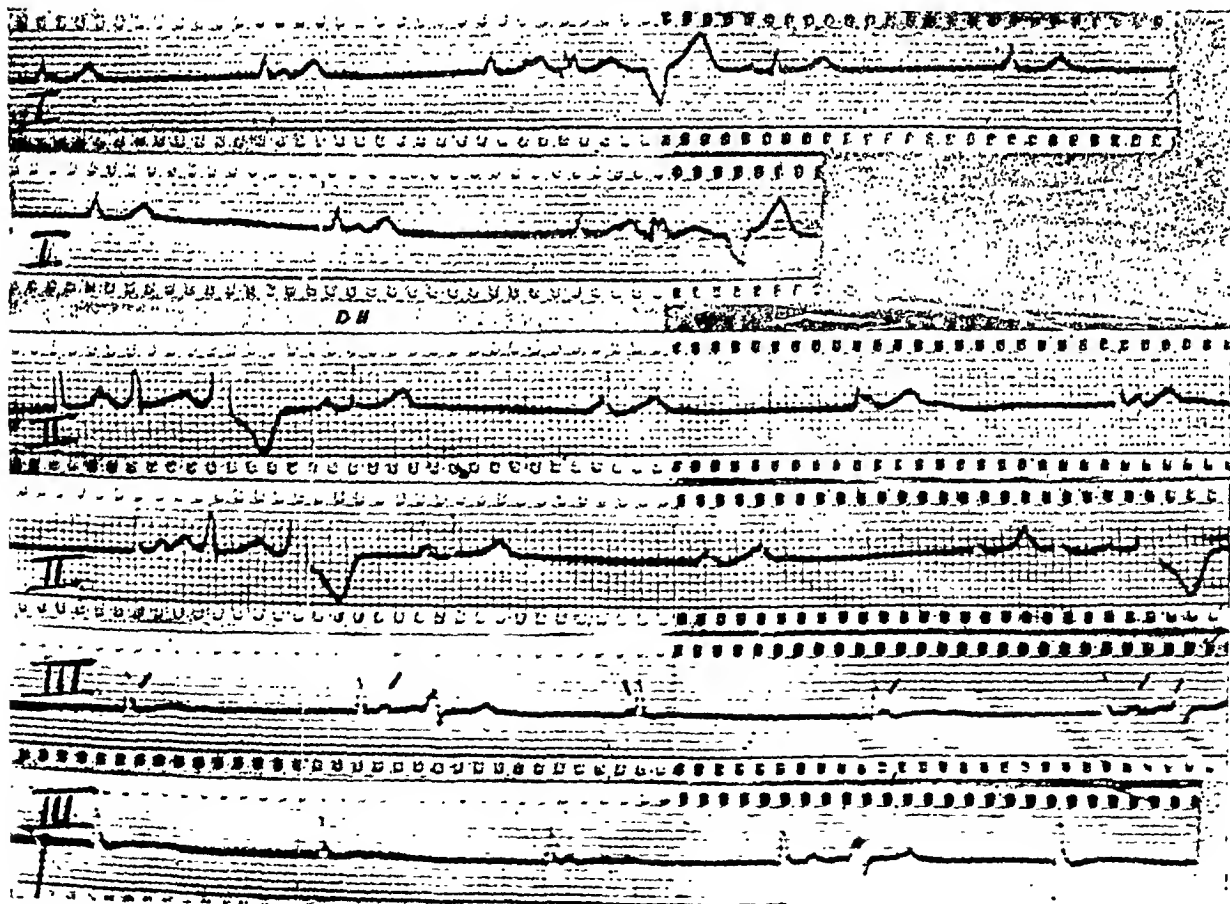


FIG. 1.—Electrocardiograms showing complete heart block with frequent ventricular extrasystoles, and the ventricular rate (about 40) slightly faster than the auricular rate (about 39 a minute).

dyspnœa increased during exertion. Her heart beats were irregular on account of extrasystoles. Her pulse rate was 40. This bradycardia was a serious symptom. On examining her lungs we found some dry rales. Her blood pressure was 200/100 with the Vaquez apparatus. There was nothing important in her other organs. The urine was normal. The Wassermann and Kahn reactions were negative.

The most important findings were in the cardiogram (Fig. 1). Extrasystoles appeared after four or five ventricular beats. The number of the regular beats were 40 a minute. There was an important bradycardia caused by complete heart block, because the auricular beats were independent of the ventricular beats. One point attracted our special attention, namely, that the number of the auricular beats were 39 and the ventricular beats 40 a minute. Indeed, in complete heart block it should be the contrary, with the auricular beats from about 60 to 80 and the ventricular beats about 35 a minute. So a complete heart block was combined with slowness of the auricular rate. What could be the cause of this slowness? The following diseases must be considered: cerebral tumour, meningitis, cerebral commotion, cholæmia, digitalis intoxication, typhoid fever, hypothyroidism, vagotonia, and last, coronary sclerosis. In our case only two things seemed to be possible: (1) vagotonia, or (2) the destruction or degeneration of the Keith-Flack node.

In order to discard the first possibility we injected atropine and adrenaline and afterwards we took a new cardiogram (Fig. 2). These medicaments did not change the slowness of the

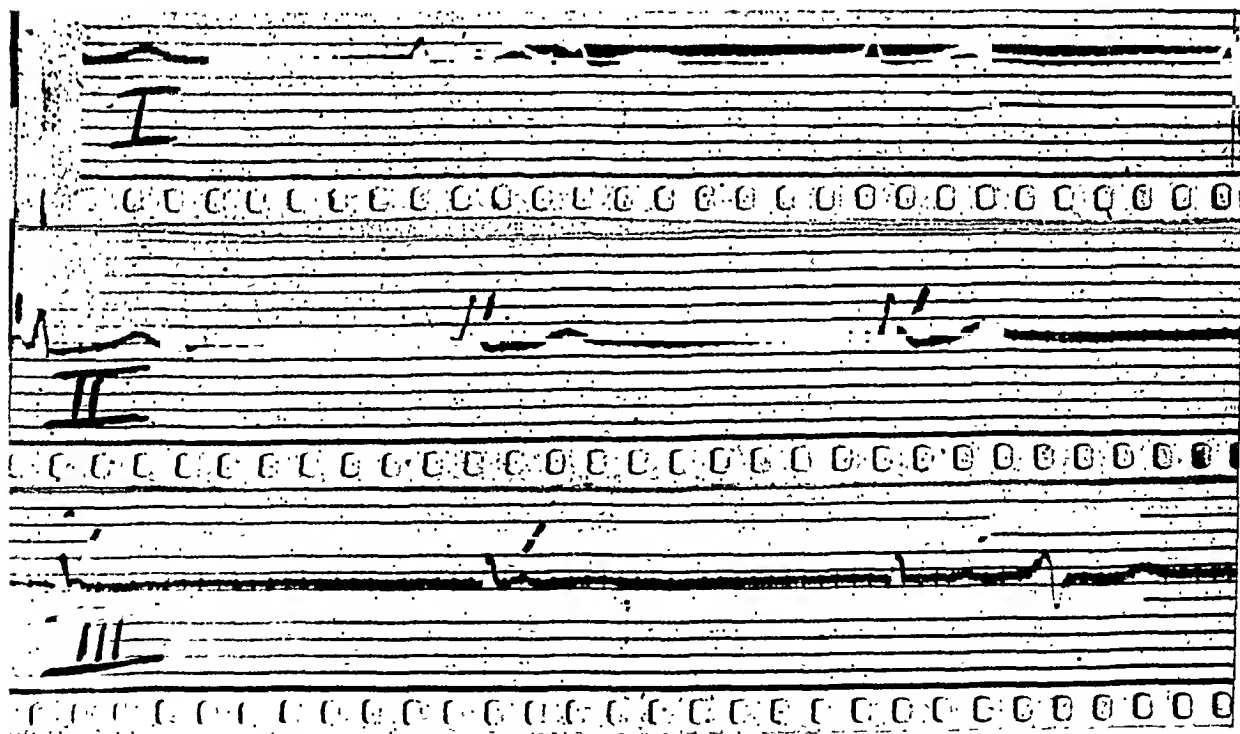


FIG. 2.—Electrocardiograms after the injection of atropine and adrenaline, showing no significant change in the slow auricular rate.

auricular beats. Therefore we decided that it was not the result of vagotonia, but of a coronary sclerosis. The coronary arteries being unable to vascularize the Keith-Flack node, the excitation produced was under the normal rate.

This form of complete heart block with slow auricular beats is very rare. Some parts of the records taken with Siemens apparatus appeared somewhat like fibrillation or nodal rhythm, but the figure as a whole show that it was an example of complete heart block.

Further records were not possible because the patient died. At the section of the body we found a diffuse myocarditis.

SUMMARY

A case of complete heart block with a rare degree of auricular bradycardia is described. The ventricular rate was 40 and the auricular rate 39 a minute.

As the auricular rate was not influenced by atropine or adrenaline it was thought to be due to coronary disease and not to increased vagal tone.

FREDERICK JOHN POYNTON

F. J. Poynton, son of the Rev. F. J. Poynton, rector of Kelston, Bath, was born in 1868 and died on October 29, 1943. He and his elder brother, A. B. Poynton, formerly Master of University College, Oxford, were both educated at Marlborough, in the welfare of which he remained keenly interested. He felt that he owed to one of his form masters there the impulse to take up his active medical career.

He started his medical studies at University College, Bristol, and won a scholarship at St. Mary's Hospital, London, in anatomy and physiology. Qualifying in 1893, he gained first-class honours in the London M.B. the following year, took the M.D. in 1896, and was elected F.R.C.P. in 1903.

In 1900 Poynton became physician to out-patients at the Hospital for Sick Children and in 1903 assistant physician to University College Hospital. His work was done at these two hospitals with which he remained connected till the end of his life, though when he retired from the active staff in 1934, he went back to live near Bath, at Coombe Park.

Poynton will be mainly known for his work with Paine, trying to show that rheumatic fever with chorea was a specific infective disease and that it was caused by the *Diplococcus rheumaticus*. The latter part of this view was never widely confirmed and has not been accepted, and this has perhaps obscured a full appreciation of his other work bearing on acute rheumatism. When the time comes for a full understanding of the cause of acute rheumatism, it may be that his work will be found to have been along the right lines even if there were errors in the bacteriological technique.

His research work may be divided into these main stages. First in papers with Lees (*Medico-Chir. Trans.*, 81, 419, 1898) and Still (*Trans. Path. Soc. London*, 50, 324, 1899) and others, he dealt with the dilatation of the heart and the changes in the muscle during rheumatic fever, and with the histology of the rheumatic nodule, arguing from these that rheumatism was of infective origin. There are also statistics of some measurable features of rheumatism in children and good clinical observations—data which have helped to establish modern clinical views.

The second stage, in association with Paine, dealt more directly with the discovery of the *Diplococcus rheumaticus*. His first paper published in 1900 (*Lancet*, 1, 1352) represented some years intensive search for the infecting organism and results were not published until they had found it in the pericardium, in the heart muscle, in the joints, and in the rheumatic nodule, and until they had reproduced a good imitation of the disease in rabbits (an animal that has unfortunately proved itself a most unreliable guide for human pathology).

In the last group of his publications many of the papers are now of less interest as they were concerned with criticisms that had been made of the *Diplococcus rheumaticus* and with his rather too ardent defence of the work by himself and Paine. There are, however, others of more general clinical interest. One dealt with 52 of his cases of acute rheumatism in children under 5 years, 43 of them having heart disease: the features of rheumatic and pneumonic pericarditis were also contrasted (*Quart. J. Med.*, (1908) 1, 225). Another on so-called scarlatinal rheumatism brought forward evidence that the disease is identical with ordinary rheumatic fever, having followed and complicated the original scarlet fever—a view which has now gained general acceptance (*Quart. J. Med.*, (1909) 3, 15). Another discussed his view that malignant endocarditis might sometimes be rheumatic (*Quart. J. Med.*, 5, 463, 1912) but he failed perhaps to prove that there was not a combination of a terminal infection on an old rheumatic valvu-

litis. Yet this paper does show the importance of rheumatism as a cause of aortic valvular disease which has sometimes been overlooked or minimized.

In 1931, with Bernard Schlesinger, he published a book on *Recent Advances in the Study of Rheumatism*. He also wrote a small book on *Heart Disease and Thoracic Aneurysm* (1907) and with Paine republished many of his papers with the title *Researches on Rheumatism* (1913), a work dedicated to Lees, his friend and teacher. He ended this with a chapter on the prevention of acute rheumatism from which the following quotations are taken. He would, I think, have been pleased with the short review and the joint report on the Care of Rheumatic Children that follow this article.

"The importance of the prevention of an infection which is the great cause of organic heart affections in the young is one that cannot be over-rated; and we believe that definite results will be forthcoming because acute rheumatism is met with much more frequently among the poorer classes and is encouraged by those agencies, which may be summed up in the single word 'poverty.'

"In the great hospitals it is clear that we possess ample means for treating the acute disease and its complications and for advancing its study in many directions. Their value might well be strengthened in the future by the establishment of some special convalescent homes in carefully chosen sites for those recovering from early rheumatism including heart disease and chorea.

"We are convinced that the medical inspection of children in the State schools will in the near future provide us with valuable information upon the influence of school life on chronic rheumatic heart disease and on the relation of out-breaks of acute rheumatism to epidemics of sore throats.

"The education of parents and school teachers in the principal dangers of acute rheumatism might well be carried on by means of simple instructions and lectures. Among such instructions may be suggested the following for rheumatic children.

1. The importance of proper clothing.
2. The care of sore throats.
3. The necessity for attention to 'growing-pains.'
4. The importance of undue nervousness, clumsiness, and night-terrors, as warnings of chorea.
5. Parents should be warned that the early signs of heart disease are few, and that shortness of breath is more often complained of than pain.
6. Much emphasis should be laid upon need for patience when a child is recovering from heart disease.
7. Parents should be told that rheumatism is very liable to recur.

"We believe that more attention might be given to the condition of the tonsils and naso-pharynx in the rheumatic child, and also to the choice of an employment for those who have been damaged by the disease.

"The view that acute rheumatism is an infective disease raises again the important questions of climatic and local surroundings, sanitation, and conditions of housing. The possible relation that it may bear to other infective processes seems worthy of further inquiry.

"It is to *prevention*, then, that we look for some advance from this grievous state of affairs, and to this pressing need that we have ventured to publish this book."

Poynton never became deeply interested in modern cardiology and despite so much devoted and passionate work on the heart in rheumatism he was primarily a children's physician. It was here that he was at his best and his real understanding of the child as well as of its disease ensured his success, which was widely recognized as when he became President of the British Pædiatric Association in 1931.

Poynton was a good teacher and as one writer has said "His mischievous frankness of speech endeared him to students." He was also a good chairman of committees and was Senior Censor of the Royal College of Physicians in 1930.

He was a man with many interests and had been a fine cricketer who played for Somerset from 1891 to 1896; he also played hockey for Middlesex. He had a great love of music and a good tenor voice inherited from his parents. I am indebted to his friend Sir Henry Tidy for permission to quote the following appreciation, published in the *British Medical Journal*.

"Poynton was a character and sometimes appeared almost wishful to be an oddity. He was a countryman, and deliberately retained a countryman's characteristics with a certain scorn of personal appearance.

Short and stocky in build, he was enormously strong. He held the curious record of captaining a first-class county cricket eleven after attaining to the sober dignity of a Fellow of the College of Physicians. His outstanding cricketing feat was achieved in two hours at Hove

when he and Sammy Woods scored 305 runs at top speed for Somerset against Sussex, and he loved to recall the episode. He played hockey for Middlesex and had some skill at real tennis. He had a fine tenor voice and sang for many years in the choir of St. James' Church.

Unfortunately he allowed his professional life to be clouded by what he considered to be the unsympathetic attitude of the profession towards his researches on rheumatic fever, though his resentment never extended to individuals. When speaking in public and at medical meetings he seemed to delight in supporting some illogical standpoint, and while he amused his audience he was not taken very seriously. But when he dealt with a sick child he had a knack of talking spontaneously as if they were equals, and every child felt at ease with him.

He was a delightful personal friend and a great companion on a holiday. He enjoyed every moment, and to the end he retained his power of boyish enjoyment, his sincerity and his honesty and his love of children."

MAURICE CAMPBELL.

THE CARE OF RHEUMATIC CHILDREN

REPORT BY THE CARDIAC SOCIETY AND BRITISH PÆDIATRIC ASSOCIATION

In 1942 the Cardiac Society appointed a small committee to draw up a report and make suggestions about the arrangements that should be made for the care of rheumatic children. When it was learnt that the British Pædiatric Association had appointed a similar committee and that some members were serving on both bodies it was hoped that a joint report might be made. This wish was shared by the British Pædiatric Association and the two committees met again as a joint committee and drew up a report. After various minor modifications the Council of the Cardiac Society and the Executive of the British Pædiatric Association agreed to publish the report that follows. They are greatly indebted to the following members who drew up the original joint report:

F. M. B. Allen (B.P.A.), J. V. Braithwaite (B.P.A.), T. F. Cotton (C.S.), W. Evans (C.S.), C. B. Perry (B.P.A. and C.S.), C. T. Potter (B.P.A.), J. C. Spence (B.P.A.), A. G. Watkins (B.P.A.), K. D. Wilkinson (B.P.A. and C.S.), T. P. Williams (B.P.A.), and B. Schlesinger (C.S.) (who was prevented from agreeing to the final draft owing to absence on active service).

Acute rheumatism is primarily a disease of school age and often produces serious results. It impairs physical health, causes serious loss of education by preventing attendance at school, is the main cause of organic cardiac disease in early life, and may lead to physical incapacity for years and to death relatively early in adult life. Until it is possible to prevent children becoming the victims of this disease, treatment must be limited to early diagnosis and the use of those measures which are known to hold out the best prospects of limiting the cardiac damage.

These objects can best be effected by the following:—

- (1) The establishment of cardio-rheumatic clinics where the diagnosis can be established early and with certainty.
- (2) The organization of hospital schools where children can be efficiently treated for so long as may be necessary while education continues.
- (3) The compulsory notification of all cases of acute rheumatism, chorea, and rheumatic heart disease.

These steps may ultimately prove desirable for the whole country. At the moment, however, it is suggested that a trial should be made in certain selected centres (e.g. large towns with medical schools) where suitable personnel for staffing clinics and hospital schools would be available. *It must be stressed that these three actions must be taken concurrently and that there would be no object in setting up notification if no clinic were established or in starting a clinic unless it has access to a hospital school.*

THE CARDIO-RHEUMATIC CLINIC

This should be situated in such a position that it is easy of access from the surrounding district. It should be closely associated with a key hospital, so that good laboratory facilities may be readily available, and the clinical material of the clinic may be utilized for teaching purposes. It should be purely consultative and advisory, with the objects of diagnosis and

supervision, of follow-up, of research, and possibly of the direction of adolescent patients into suitable occupations.

Consultations should be by appointment (where necessary transport should be provided), and school medical officers and general practitioners should be encouraged to attend. The clinic should be held at least once a week, and when needed an evening session should be arranged to meet the requirements of patients in employment. The follow-up and supervision should continue into adult life. This clinic should be staffed by physicians with experience of children's diseases and diseases of the heart. This is essential to enable the clinic to deal with problems arising in the differential diagnosis of rheumatic manifestations and to follow up cardiac cases into adult life. In some centres it may be possible to find one physician who combines these functions, but in others it will be necessary to make use of a team. They should have the help of an assistant physician or registrar. An almoner should be attached to the clinic and adequate secretarial assistance must also be provided. It is desirable that the equipment should include: apparatus for measuring height and weight; an X-ray set for screening and photographing hearts; an electrocardiograph and a technician; a laboratory for sedimentation rates, blood counts, biochemical investigations, etc.

The function of this clinic should be the early diagnosis of acute rheumatism in children and adolescents, and the follow-up of those patients who have had carditis, with the following objects.

- (1) Securing the best possible treatment so as to minimize cardiac damage.
- (2) Supervising the life and activities of the rheumatic child.
- (3) The compilation of reliable data with the object of securing the prevention of acute rheumatism.
- (4) The direction of cardiac defectives into suitable occupations.
- (5) The education of medical practitioners in the diagnosis of acute rheumatic carditis and cardiac disease generally.
- (6) The differentiation of habit spasms and tics from chorea, and "growing pains" from acute rheumatism, which experience has shown form a large part of the work of such a clinic.

Consultations at the homes of children should be made possible. The parents, the family doctor, and the school medical officer should be advised as to fitness for school and any treatment needed. A report should be sent to the family doctor and to the school medical officer.

All cases of acute rheumatism, chorea, and carditis notified should be immediately referred to the clinic unless admitted to the hospital school. School medical officers and general practitioners should be authorized and encouraged to refer to the clinic all children under the age of 16, in whom cardiac murmurs of doubtful significance are found. This is important for two reasons:—

- (a) There is often difficulty in deciding whether a given murmur is evidence of past or present carditis or a congenital malformation, or is an "innocent" or "functional" murmur; it is most important that any such doubt should be removed so that unnecessary restrictions need not be imposed.
- (b) The proper examination of such cases has a great value from the point of view of research and education.

It is desirable in addition that all children with a history of past rheumatism or chorea, even though they have no signs of cardiac damage, should also be referred to the clinic so that they may be kept under supervision and any relapse noted as soon as possible.

In addition to the report and advice on school and treatment a note should be made as to the necessity for another examination (i.e. in 6 weeks, 3 months, 6 months, etc.) and arrangements made for the child to be summoned to the clinic again at that time.

HOSPITAL SCHOOLS

Such hospitals should be established at suitable points throughout the country. They should be hospitals for treatment of children with cardiac rheumatism, but should also be equipped with well-qualified teachers and full school apparatus so that educational facilities may be available for all those inmates who can benefit by education. In addition to continuing general education, each child should be trained as far as may be possible so that he is able to earn a living without the necessity of laborious physical work. By various grades of recreational education both knowledge and manual skill may be acquired.

Where possible these schools should be situated in the country, and they should be large enough to accommodate all cases of acute rheumatism arising in the district served. The stay of each child should be a period of many months. Each hospital school must be supplied with adequate hospital equipment so that nursing of severely ill children can be carried out and so that progress may be recorded—i.e. an electrocardiograph and a technician, an X-ray screen and a suitable laboratory. Each should be a centre for research into ætiological factors and improved treatment of acute rheumatism. In these hospital schools the treatment of acute rheumatism might well be combined with that of other “long stay” children’s diseases. This may be particularly necessary in view of the probable shortage of skilled teachers of the necessary type since it is clearly desirable that *all* children suffering from long illnesses should be provided with educational facilities.

Where possible the physician in charge of the cardio-rheumatic clinic should also visit and supervise the hospital school and the assistant physician or registrar should also be attached to the hospital school.

Children will be admitted to the hospital school either direct from their homes immediately on notification, from other hospitals, or from the clinic, and patients should be retained in the hospital school until either (a) their condition is proved not to be due to acute rheumatism or other cause of cardiac damage or (b) it is certain that the infection is quiescent or the condition cured, and the child is fit to live at home. On return they should, whenever possible, attend ordinary schools. Experience has shown that unless there is considerable cardiac enlargement these children are well able to lead a normal school life with full activities. Cases with more severe cardiac damage can attend ordinary schools provided they do no competitive games or drill. P.D. schools of a special type may be of great value by enabling education to continue until the age of 16 and by providing a special vocational training in the final years. But it must be remembered that it is most desirable from the psychological point of view that these children should be brought up as much like normal children as possible. A small number of children may be so severely damaged that it is advisable to transfer them to an institution for chronic invalids if they cannot be adequately cared for at home. Immediately on discharge from the hospital school the child should be referred back to the clinic for supervision.

In view of the striking social incidence of acute rheumatism every effort should be made to promote satisfactory housing for all children and to see that all children receive adequate diet and clothing. Children who have had acute rheumatism should be given special home visits with supervision, and improvement of home environment whenever possible.

The public and the profession should be educated to realize the potential importance of upper respiratory infection however trivial it may appear. Parents of children attending the supervisory clinics should be instructed to report any such infection at once so that proper care may be instituted in an attempt to prevent a rheumatic relapse.

OTHER MEASURES

Vocational Training.—Facilities must be made available for vocational training of rheumatic children during their last years at school and on leaving school so that they are trained for

suitable sedentary employment. When this has been done steps must be taken to ensure that when they start work they do in fact obtain such employment.

Notification—The serious results of rheumatic carditis and the importance of early diagnosis and adequate treatment make it imperative that *all cases of suspected acute rheumatism, chorea, and rheumatic heart disease in children under the age of sixteen years* should be made compulsorily notifiable.

It should be the duty of any medical practitioner who suspects that a child or young person is suffering from any of the above-named conditions to notify immediately the local Health Authority.

It should be the duty of the local Health Authority upon the receipt of such notification to refer the child to a cardio-rheumatic clinic, and if necessary to offer to the parents accommodation for the child in a hospital school. It should be possible for the notification to be cancelled if, after examination at the clinic, it is found that the child is not suffering from rheumatism, chorea, or rheumatic heart disease.

Research.—All clinics and hospital schools should be so staffed and equipped that they become active centres of research. This research should be co-ordinated by frequent interchange of ideas amongst the staffs of the various regions. This could perhaps be best facilitated by a co-ordinating committee who should be informed of all research in progress.

SOCIAL AND ECONOMIC CONDITIONS AND THE INCIDENCE OF RHEUMATIC HEART DISEASE

BY

G. H. DANIEL

It has not been the custom of this Journal to review papers of cardiological interest. However this paper, published in the *Journal of the Royal Statistical Society* (1942) 105, 197, seems to justify making an exception, as it is pertinent to the preceding report and may not have been easily available to all who are interested.

That rheumatic fever and mitral stenosis are more common among the poor than the rich is accepted teaching, supported by much experience and statistical evidence. This, however, fails to show if the difference is due to the effect of income on diet, or on housing, or on other conditions of the environment—material or mental—or might even be explained by hereditary factors. A much more detailed statistical analysis would be needed to isolate these facts.

The Medical Research Council's Report of 1927 sought to evaluate the effects of social and economic conditions by comparing the living conditions of 721 families with children attending hospital for rheumatism with those of 200 families with children attending hospital for non-rheumatic diseases. Of this Daniel says: "It is quite possible that their diseases as well as those of the rheumatic families were related to adverse social and economic circumstances. In that case, comparison could not be expected to reveal the importance of those conditions. The rheumatic families should be compared with the total population."

In 1937 the University of Bristol with the Colston Research Society investigated the circumstances of a random sample (one family in twenty-two) of the Bristol working class population. With the data available the opportunity was taken of comparing the incidence of rheumatism with some of the other social and economic factors; rheumatic heart disease was taken as the significant evidence because this was a more precise criterion.

The number of rheumatic families in each class was divided by the number of families from the sample of the total working-class population in the same class and, to facilitate comparison of incidence between the classes, the result was expressed as a percentage of the proportion between all 341 rheumatic families and 1424 families in the total population sample. This gave for each class the incidence of the disease as a percentage of the average incidence among the entire population studied.

The Bristol data thus yield the following information:

- (a) Incidence of rheumatic heart disease in each group of working-class families as a percentage of the average incidence for all Bristol working-class families. This will be taken as the dependent variable (Y) and for the sake of brevity it will be referred to as the "incidence."
- (b) Income available for expenditure on food, clothes, and fuel as a percentage of minimum needs. This independent variable (X1) will be referred to simply as the "net income." It is not, of course, the total family income that is likely to affect susceptibility to disease, as much as the income relative to the needs of the family.
- (c) Number of rooms per person (X2).
- (d) Use of a basement room, receipt of meals or milk at school, and membership of a doctor's club.

The conclusions reached about (b) and (c) are shown in Tables I and II.

TABLE I

INCIDENCE OF RHEUMATIC HEART DISEASE IN RELATION TO NET INCOME

| Net income (as a percentage of minimum needs) | Families with rheumatic heart disease | Families in sample of total working-class population | Incidence of rheumatic disease (as a percentage of average incidence) | Expected incidence* |
|---|---------------------------------------|--|---|---------------------|
| Under 100 | 77 | 232 | 139 | 142 |
| 100-120 | 54 | 152 | 148 | 122 |
| 120-140 | 51 | 191 | 112 | 108 |
| 140-160 | 33 | 192 | 72 | 97 |
| 160-180 | 37 | 192 | 81 | 88 |
| 180-200 | 31 | 149 | 87 | 81 |
| 200-220 | 17 | 93 | 76 | 75 |
| 220 and over | 41 | 223 | 77 | 70 |
| Total | 341 | 1424 | — | — |

* Estimated from $Y=4291 X_1^{-0.757}$

TABLE II

INCIDENCE OF RHEUMATIC HEART DISEASE IN RELATION TO THE NUMBER OF ROOMS PER PERSON

| Rooms per person | Families with rheumatic heart disease | Families in sample of total working-class population | Incidence of rheumatic disease (as a percentage of average incidence) | Expected incidence* |
|--------------------|---------------------------------------|--|---|---------------------|
| Under 0.6 | 52 | 130 | 167 | 187 |
| 0.6-0.8 | 69 | 193 | 149 | 136 |
| 0.8-1.0 | 53 | 194 | 114 | 107 |
| 1.0-1.2 | 73 | 335 | 91 | 89 |
| 1.2-1.4 | 59 | 303 | 81 | 76 |
| 1.4-1.6 | 10 | 71 | 59 | 66 |
| 1.6-1.8 | 19 | 138 | 58 | 59 |
| 1.8 and over | 6 | 60 | 42 | 53 |
| Total | 341 | 1424 | — | — |

* Estimated from $Y=95.1 X_2^{-1.037}$.

The information gathered about the living conditions of the Bristol working-class population allows the following conclusions to be drawn.

- Differences in incidence of rheumatic heart disease between sections of this population were associated with differences in the family income available after paying for rent, rates, travelling, and other fixed items, expressed as a percentage of minimum needs.
- Considerable differences in incidence corresponded closely with the variation in the number of rooms used by each family divided by the number of persons in the family.
- Families which belonged to doctors' clubs suffered less from the disease than did the remainder of the population.
- There is an indication, though the results are not statistically significant, that families which lived or slept in basement rooms included more cases of the disease than other families.
- Each one of these relations was true independently of the others.

To what extent these findings based on the Bristol 1937 experience apply to the population of the whole country is unknown. But Bristol is a large town, and there is no apparent reason why the relations found should be confined to it.

This short summary and extract will give some idea of the care with which conclusions have been reached, and may refer some who are interested to the original paper.

MAURICE CAMPBELL

UNUSUAL ELECTROCARDIOGRAM IN DEXTROCARDIA

BY

J. M. HOLFORD

Received February 4, 1944

The case here described was found in the course of a mass radiographic survey.

Case History.—The patient was a well-grown man aged 35 years. He was free from symptoms. He had no significant past medical history. He had always lived a normal life and had been moderately athletic in his school days.

On clinical examination it was found that cardiac pulsation was palpable in the right fourth intercostal space just internal to the mid-clavicular line. Normal heart sounds were heard in this area and between it and the sternum. At the left border of the sternum sounds were faint and further to the left were inaudible. No bruits were heard. There was no dyspnoea, cyanosis, clubbing of the fingers, or other indication of cardiac disorder. Blood pressure was 120/70.

Radiography showed a heart in the position of complete dextrocardia, but otherwise of normal contour. The lung fields were clear. The left dome of the diaphragm was raised. The liver and stomach were not transposed.

Electrocardiographic Findings.—A cardiogram consisting of the three standard limb leads and three chest leads is shown in Fig. 1.

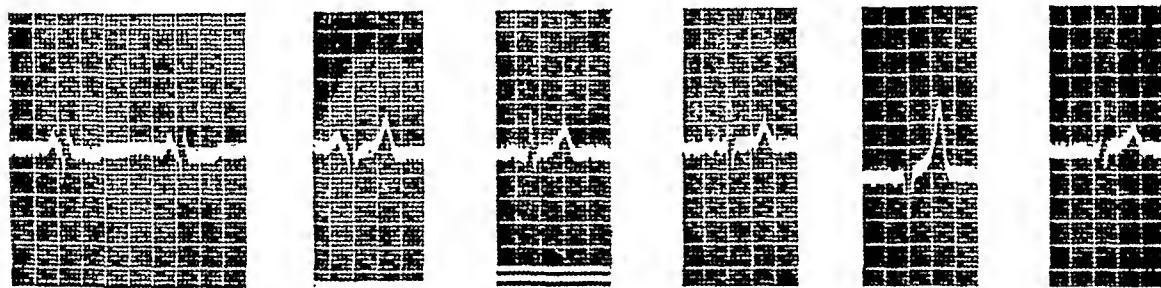


FIG. 1.—The standard leads I, II, and III are followed by CF1, CF2, and CF4 in that order, reading from the left. The chest leads have been taken in the mirror image of the normal position; thus, in CF1, the chest electrode is at the left border of the sternum, in CF2 at the right border, and in CF4 in the right mid-clavicular line; the neutral electrode is on the right leg.

In lead I, P is upright, the QRS complex shows a downward deflection followed by an upward one of approximately equal magnitude, and T is shallow and diphasic. All the remaining leads appear normal.

In their paper on the normal electrocardiogram Chamberlain and Hay (1939) gave no instances of an inverted P wave in lead I, though it was sometimes so small as to be hardly visible. The accepted finding in dextrocardia, with or without situs inversus, is inversion of all waves in lead I. Katz (1941) and Pardee (1942) in their standard text-books of electrocardiography mention no other departure from the normal. Gross (1941), reporting four fresh cases in the course of a comprehensive review of dextrocardia, appears to regard complete inversion in lead I as an invariable accompaniment of the condition. Beaujeu

and Benmussa (1939), writing from Tunis, where dextrocardia is alleged to be much commoner than in Europe, have observed upright P waves in lead I in a case complicated by the tetralogy of Fallot; they specifically state, however, that this does not occur in the absence of congenital heart disease. The low voltage T waves in lead I in the present case are also not mentioned by any of these writers.

I have to thank Surgeon Rear-Admiral F. J. D. Twigg for permission to publish this case.

REFERENCES

- Beaujeu and Benmussa (1939). *Arch. Mal. Cœur*, 32, 141.
Chamberlain, E. N., and Hay, J. D. (1939). *Brit. Heart J.*, 1, 112.
Gross, L. (1941). *J. med. Soc. New Jersey*, 38, 354.
Katz, L. N. (1941). *Electrocardiography*, London, p. 269.
Pardee, H. E. B. (1942). *Clinical Aspects of the Electrocardiogram*, 4th edition, London, p. 256.

AURICULO-VENTRICULAR RHYTHM

BY

R. A. MILLER

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Auriculo-ventricular rhythm is a relatively uncommon and obscure disorder of the heart beat, only diagnosed by means of the electrocardiogram. It occurs when the A-V node assumes control over the ventricles. When this happens, two types of auriculo-ventricular rhythm may arise. One is called A-V nodal rhythm and is recognized by the inverted P waves, which are as a rule either abnormally close to the QRS complex or may follow it. The second type of auriculo-ventricular rhythm is known as A-V dissociation, characterized by the rate of the ventricular contractions being slightly faster than those of the auricles so that there is no constant P-R or R-P interval. Theoretically, the difference between the two rhythms is due to retrograde conduction being present in A-V nodal rhythm in order to allow the auricles as well as the ventricles to respond to the new pace-maker in the A-V node, while in A-V dissociation retrograde conduction from A-V node is blocked so that the auricular contractions must arise above the A-V node, probably in the sino-auricular node (Cutts, 1937; Richardson, 1922). When ventricular bigeminy complicates A-V rhythm it is described as ventricular interference: as reciprocal rhythm when it occurs with A-V nodal rhythm, and as pseudo-reciprocal rhythm when it accompanies A-V dissociation.

To obtain a fuller understanding of these rhythms a record of thirteen such cases will be given and their unusual features will be discussed under the following headings: contributions to ætiology, the mode of onset of A-V rhythm, the significance of associated symptoms, and the value of tests used in differentiating the underlying mechanism of the disorder. Before entering upon any discussion or drawing any conclusions upon the present work, a brief account of the salient features of six of the present series of cases will be related.

CASE HISTORIES

Case 1.—Mr. S. C., aged 20, had subacute rheumatic fever and exhibited nodal rhythm for at least four months, 15/10/41 to 5/2/42. The disorder was associated with aortic and mitral disease, and exercise, atropine, and vagal stimulation were all able to produce normal sinus rhythm. The exercise consisted of doing 9512 ft.-lb. work in two minutes. The dose of atropine was 1/30 of a grain given intravenously. The result of the vagal pressure test is recorded in Fig. 1. This shows nodal rhythm,

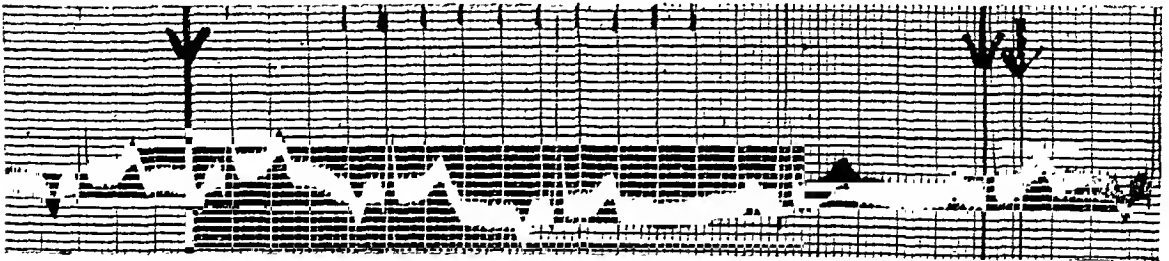


FIG. 1.—*Case 1.* Nodal rhythm changing to normal sinus rhythm by means of carotid sinus pressure, which was maintained between the single thick vertical line and the double thick vertical lines, marked with arrows. The time-marker shows 1/5 and 1/25 sec.

rate 80, followed by normal sinus rhythm when the heart rate had fallen to 50 beats a minute. This change occurred after the application of vagal pressure which is indicated by a thick vertical line. Immediately vagal pressure is removed (denoted by a pair of thick vertical lines) the heart rate rises and the nodal rhythm reappears.

Case 2.—Mrs. M. J., aged 42, came under observation because of faints. Clinically, however, there was no evidence of organic disease, nor did her electrocardiogram (Fig. 2A) signify any cardiac

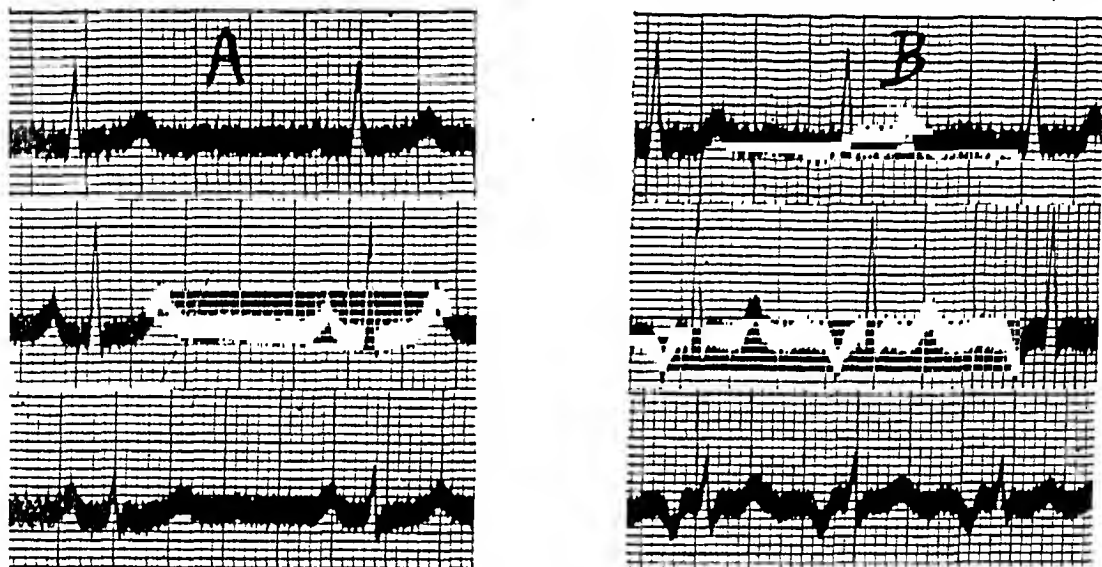


FIG. 2.—Case 2. (A) Normal sinus rhythm. (B) A-V rhythm after exercise.

lesion. The same day she did 4694 ft.-lb. work in two minutes and temporarily developed nodal rhythm (Fig. 2B).

Case 3.—Mr. A. F., aged 57, was admitted to hospital on 19/1/40 with essential hypertension and congestive heart failure. At first he had normal sinus rhythm, but later it was converted to A-V dissociation with digitalis therapy. When A-V dissociation was present on 6/2/40 and 16/11/40 the patient was nauseated with digitalis and the drug was withheld while the action of intravenous atropine, 1/50–1/30 grain, was studied on five occasions. In no instance did atropine abolish the abnormal rhythm, but on each occasion the rhythm was complicated by intermittent ventricular bigeminy (Fig. 3A) 62–90 seconds after the injection, and it lasted approximately 22–27 seconds.

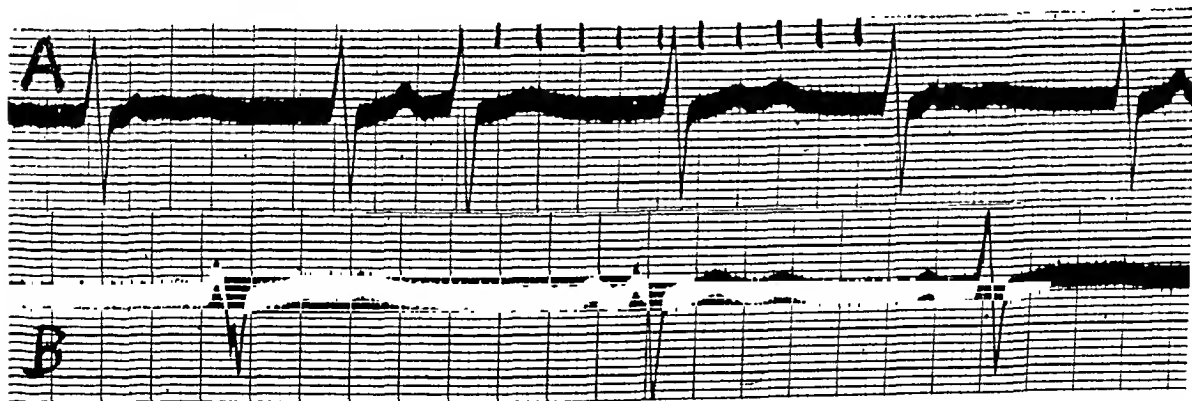


FIG. 3.—Case 3. (A) A-V dissociation with intermittent ventricular bigeminy due to atropine administration. (B) A-V rhythm with three distinctive ventricular complexes.

During this period the ventricular rate was 43–54 beats a minute. It was also noted that there were three ventricular rhythms characterized by their three distinctive QRS complexes and by their inherent rates of 35.8, 41.7 and 37.5 (Fig. 3B), but it was only the last one that was associated with ventricular bigeminy.

Case 4.—Mr. W. B., aged 49, demonstrates how either exercise or atropine abolishes auriculo-ventricular rhythm in an apparently healthy man who probably had the cardiac disorder for 25 years. He had complained of palpitation since he was nine years old and owing to D.A.H. he was discharged

from the Army during the 1914-18 war. At the time of the present observations he still had palpitation and was unduly short of breath on exertion. On examination in 1942 he was a plethoric type of man, but otherwise fit. Electrocardiographically he had nodal rhythm which slowed two or three beats a minute with either right or left carotid sinus pressure. Exercise, amounting to 9861 ft.-lb. work in two minutes raised the heart rate from 65 to 93 and at the same time normal sinus rhythm appeared. Intravenous atropine, 1/30 grain, had the same effect as the exercise test.

Case 5.—Miss M. R., aged 7, was physically fit, but clinically and radiologically there was evidence of a congenital heart with a septal defect. She was proved to have auriculo-ventricular rhythm of long standing, but normal sinus rhythm and sino-auricular block temporarily interrupted it. She was examined on seven occasions when her dominant rhythm was auriculo-ventricular complicated by ventricular bigeminy (Fig. 4A). The latter appeared when the ventricular rate ranged from 42 to 56 provided the Q-P interval was over 0.24 second.

The reaction of the abnormal rhythm to an augmented heart rate was to produce normal sinus

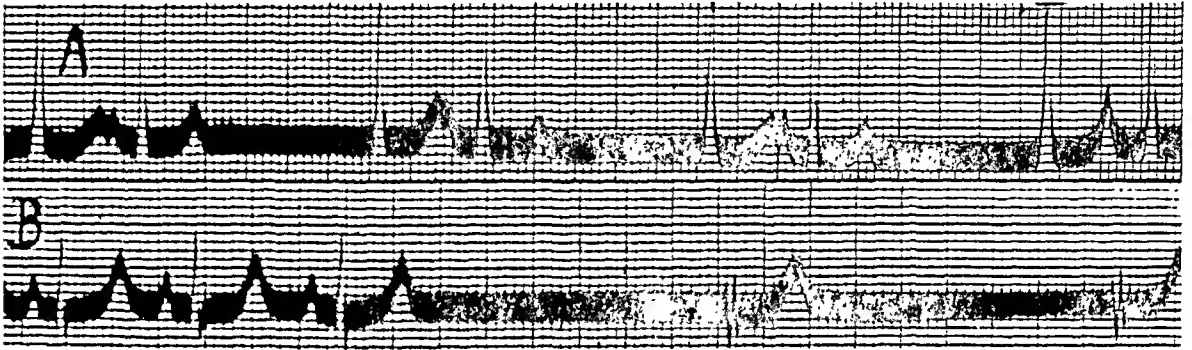


FIG. 4.—*Case 5.* (A) Auriculo-ventricular rhythm with ventricular bigeminy. (B) After physical exercise she developed normal sinus rhythm which was terminated by sino-auricular block and A-V rhythm.

rhythm; this was done on 6/6/41, after the patient had performed 2188 ft.-lb. work in two minutes: the transformation was again affected on 9/6/41 by injecting atropine sulphate, 1/100 grain, intravenously. It was strange that with the exercise test the maximum rate was not recorded immediately after the work for it rose from 64 to 108 after resting twelve and a half minutes. Yet another phenomenon occurred at this point; the normal sinus rhythm was periodically interrupted by sino-auricular block, which in turn was terminated by an idio-ventricular beat that continued to recur rhythmically for a short period at the rate of 36 to produce nodal rhythm (Fig. 4B).

Vagal stimulation did not alter the auriculo-ventricular rhythm except on one occasion when the auricular rate fell 9 beats a minute.

Case 6.—Mr. K. G., aged 25, was an apparently healthy man who for the past eight weeks had suffered from attacks of faintness and dizziness while blowing his bugle. On examination no physical abnormality was discovered. His electrocardiogram (Fig. 5) revealed normal sinus rhythm

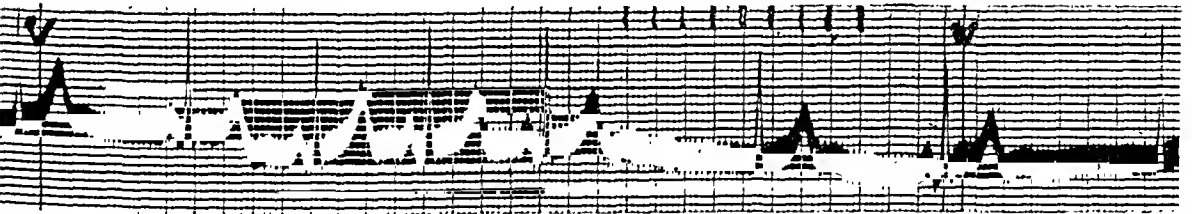


FIG. 5.—*Case 6.* Normal sinus rhythm during inspiration (marked by the thick vertical line and arrow) and A-V dissociation with expiration (marked by the second thick vertical lines and arrow).

with a heart rate of 75 following inspiration (indicated by thick vertical line), but with full expiration A-V dissociation occurred when the heart rate fell to 43 (indicated by the second thick vertical line). When exercise or atropine was given to this patient this abnormality was abolished, although sinus arrhythmia was exceptionally prominent.

ÆTIOLOGY

Both nodal rhythm and auriculo-ventricular dissociation arise through either a depression or destruction of the S-A node or else by enhancing the activity of the A-V node. Other times these factors act collectively. Such changes can be brought about by an alteration in vagal

tone (Bishop, 1921; Cutts, 1937; Gallavardin, 1920; Goodman, 1930; Resnik, 1925; Weiss, 1933), degenerative processes (Cowan, 1939), infective agents (Cutts, 1937; Reid, 1930), and by the administration of atropine, digitalis, and other drugs (Hewlett, 1923; Zeisler, 1932). The rhythm defect, however, may be missed unless exercise is given prior to the electrocardiographic investigation (Case 2).

When ventricular bigeminy complicates the A-V rhythm, the pathology and precipitating factors are similar (Bain, 1939; Bishop, 1921; Blumgart, 1930; Cowan, 1939; Cutts, 1937; Jones, 1927; Katz, 1938; Luten, 1932; and Reid, 1930; also Cases 1, 2, and 5) except that it has not been observed after exercise or with general anaesthesia (Kurtz, 1936). Doubt as to its existence in the dying heart and with asphyxia associated with Cheyne-Stokes breathing also prevails, but, in the former, A-V rhythm may be interrupted by ectopic beats with or without a compensatory pause (Sigler, 1937; Turner, 1931).

When atropine is responsible for A-V rhythm the rate may range from 52 to 100 and it may persist while the heart accelerates (Table I). The figures are obtained by taking electrocardiographic records of nine people before, during and after the intravenous injection of atropine sulphate, 1/30 grain. As intermittent observations were made after the drug had been given, the onset and termination of A-V rhythm was not always accurately known. Nevertheless, it will be seen from Table I that the rate of A-V dissociation at some time of its existence was greater than the initial heart rate. This suggests that the rhythm disorder can occur while the heart rate is augmented. This is demonstrated more conclusively in five cases (3, 6, 7, 8, and 9) where A-V dissociation was recorded while the heart rate was increasing. Such behaviour cannot be said to be due to superimposed organic disease for the disorder sometimes occurred in apparently normal subjects and because normal sinus rhythm always developed with the maximum heart rate.

TABLE I
A-V DISSOCIATION DUE TO ATROPINE ADMINISTRATION

| Case No. | Date | Remarks | Ventricular rate with N.S.R. | Ventricular rate with dissociation |
|----------|----------|--------------------------------------|------------------------------|------------------------------------|
| 3 | 4/3/40 | Hypertension in congestive failure.. | 37-60 | 55 |
| 3 | 26/11/40 | Hypertension in congestive failure.. | 37-56 | 52-56 |
| 6 | 25/3/41 | Heart normal.. .. | 57-95 | 57-83 |
| 7 | 5/9/40 | Heart normal.. .. | 79-120 | 93-96 |
| 8 | 7/6/40 | Mitral stenosis | 48-57 | 54-55 |
| 8 | 10/6/40 | Mitral stenosis | 47-60 | 54-60 |
| 9 | 27/2/40 | Bronchitis and congestive failure .. | 79-94 | 79-94 |
| 9 | 5/3/40 | After digitalization | 88-120 | 88-98 |
| 10 | 1/8/40 | Heart normal.. .. | 60-88 | 70 |
| 11 | 25/9/41 | Aortic incompetence.. .. | 62-88 | 75 |
| 12 | 16/9/40 | Angina pectoris | 66-94 | 79 |
| 13 | 8/11/41 | Hypertension and heart failure .. | 75-115 | 100 |

Therefore, in the present series of cases, atropine probably acted more rapidly upon the auriculo-ventricular node than on the sino-auricular node, so as to allow the ventricles to beat faster than the auricles and at the same time to permit both auricle and ventricles to increase their rates. This view on the dual action of atropine is not shared by Wilson (1915) who believed that A-V dissociation due to atropine was due to an initial "inverse" excitation of the vagus which was followed by the later paralytic effect.

MODE OF ONSET

It is generally believed that the transition from normal sinus rhythm to auriculo-ventricular rhythm takes place without the cognizance of the patient or doctor, for no characteristic signs or symptoms are produced. Nevertheless, suspicion of its development should be aroused

by the onset of a bradycardia. As a rule, the alteration in rhythm is accompanied by a gradual slowing of the heart rate, but in Case 5 there was an abrupt fall in the heart rate from 96 to 36 beats a minute, the change being due to normal sinus rhythm being terminated by S-Å block which was followed by an A-V rhythm with a ventricular rate of 36. A similar sequence of events has been described by Weiss and Baker (1933) in their Cases 1 and 2. They achieved the transformation in rhythm by applying carotid sinus pressure to their patients. Therefore, it is probable that alteration in vagal tone explains the change in Case 5 as well as in those mentioned by Weiss and Baker (1933).

The factors that account for ventricular bigeminy being intermittent in A-V rhythm are the rate of the heart and the refractory period of the A-V node and bundle. The latter is determined by measuring the Q-P intervals, or the time which elapses between the initial deflexion of the QRS complex and the beginning of the P wave. The shortest Q-P interval when ventricular bigeminy is present and the longest Q-P interval when the extra beat is absent, are the two important measurements, as it is somewhere between them that the refractory period lies. Details of these investigations are given on Table II and in the history of Cases 3 and 5. They may be summarized by stating firstly that a bradycardia is almost certainly essential for the development of ventricular bigeminy. Secondly, the ventricular rates during which the bigeminy appears will vary from case to case. Thirdly bigeminy is controlled by the refractory period of the A-V node and bundle. It is also clear that an increase in the heart rate is accompanied by a diminution in the refractory period which is analogous to reduction in the P-R interval when the heart rate is augmented in some people with partial heart block.

TABLE II
INFLUENCE OF HEART RATE AND Q-P INTERVAL UPON VENTRICULAR BIGEMINY

| Case No. | Date | Ventricular rate per minute | Shortest Q-P interval with bigeminy, seconds | Longest Q-P interval without bigeminy, seconds |
|-----------------------|---------|-----------------------------|--|--|
| Blumgart (Case 2) . . | 1930 | 60.0 | 0.36 | 0.32 |
| Case 3 | 13/2/40 | 55.5 | 0.32 | 0.30 |
| Case 3 | 8/2/40 | 47.6 | 0.37 | 0.35 |
| Case 5 | 6/6/41 | 45-48 | 0.34 | 0.32 |
| Case 3 | 6/2/40 | 44.1 | 0.40 | 0.40 |
| Case 3 | 8/2/40 | 42.2 | 0.46 | 0.46 |

It is now evident that ventricular bigeminy must have a complex mechanism and it probably arises through the stimulus that activates the auricle passing backwards to re-enter the ventricle to produce an extra ventricular contraction. This sequence of events is known as "re-entry" and it is preferred by most authors to the alternative theory of "parasystole." The latter is based on the supposition that there is a second automatic centre situated low down in the auricle which initiates the extra ventricular contraction (Blumgart, 1930, and Luten, 1932).

SIGNIFICANCE OF SYMPTOMS

It is uncommon for A-V rhythm to produce symptoms; palpitation, however, is sometimes reported (Cowan, 1935; Schotts, 1937; and Thomson, 1941), and it may be associated with ventricular bigeminy (Case 4). At other times faintness and giddiness occur (Katz, 1938, and Case 6) and they are probably due to the accompanying bradycardia that develops suddenly without an adequate compensatory mechanism in the cerebral or the systemic circulation. Such an explanation has been offered for similar symptoms in a person who developed a sudden

bradycardia while normal sinus rhythm was present (Turner, 1931). The prognosis in these cases is the same as for any other symptom experienced during A-V rhythm. That is to say, prognosis is determined entirely by the associated pathological process and not by the abnormal rhythm (Richardson, 1922).

THE VALUE OF TESTS IN DETECTING THE DEFECTIVE MECHANISM

Three tests have been utilized in an attempt to discover whether or not the A-V conducting tissue is defective. These tests have been developed on the assumption that acceleration of the heart tends to increase metabolic disturbances that may accentuate or reveal abnormal rhythm or conduction, while slowing the heart rate will have the opposite effect. The tests involve the use of atropine, exercise, and vagal stimulation, and are simple to perform. Unfortunately, their value is very limited on account of both vagal dysfunction and organic disease of the cardiac conducting mechanism being sometimes present (Cases 1 and 3). At other times, technical errors, such as failure to repeat a test with greater vigour or with larger doses of atropine in people with persistent A-V rhythm may give rise to fallacies.

The vagal stimulation test is performed by pressure on the carotid sinus. Normally, a heart can react in numerous ways to such a procedure. Moreover, if an alteration in rhythm is produced it cannot always be reproduced (Weiss, 1934). When vagal stimulation is utilized in the investigation of A-V rhythm, there are two responses that are informative; in one A-V rhythm persists throughout the test and is indicative of either vagal dysfunction or a cardiac lesion as the ætiological factor of the rhythm disorder (Blumgart, 1930; Dock, 1928; Luten, 1932; Thomson, 1941; Wedd, 1930; White, 1915; and Cases 4 and 9). In the other response, normal sinus rhythm develops, from which it may be concluded that organic disease of the heart is present. As far as is known, Case 1 is the only example exhibiting these features, but as he had aortic and mitral disease, the test did not aid in the prognosis and treatment of this patient. Therefore, it may be concluded from the above evidence that vagal stimulation is of little or no value in investigating A-V rhythm.

The two tests that are likely to prove of value in A-V rhythm are the exercise test and the atropine test. The former consists of making the patient do so many foot-pounds of work in a given time, while the latter is done by giving atropine, 1/60–1/20 grain, orally or subcutaneously, or intravenously (Bokspan, 1928; Goodman, 1930; Katz, 1938; Luten, 1932; Neslin, 1932; Ritchie, 1923; Wedd, 1941; White, 1915; and Cases 1, 3, 5, and 13). These tests are, however, only warranted or enlightening when the ætiology of A-V rhythm is obscure. In view of this, six apparently healthy people with A-V rhythm (Bishop, 1921; Cutts, 1937; Thomson, 1941; Williams, 1913; and Cases 4 and 6) have been studied, and it has been found that atropine abolished the abnormal rhythm in all but one instance (Williams, 1913). Therefore, the majority exhibited vagal dysfunction, which carries with it a good prognosis. This is even true should the abnormal rhythm be present for eighteen months (Thomson's Case 1, 1941) or possibly twenty years (Case 4). When organic disease is the determining factor in the production of A-V rhythm the expectation of life can not be as good, but it is possible for the rhythm disorder to persist for a year and for health to be maintained over the corresponding period of time (Williams, 1913).

SUMMARY

This paper is based on observations on thirteen cases of auriculo-ventricular rhythm, the salient features of which have been correlated with appropriate facts recorded by others. The outstanding features fall under four headings as follows.

Physical exercise may now be added to the factors that precipitate A-V rhythm. Atropine can produce the rhythm disorder when a tachycardia is present, or when the heart rate is increasing. From these observations it was decided that atropine acted simultaneously and

unequally upon the sino-auricular node and the auriculo-ventricular node in order to produce A-V rhythm.

As a rule, the onset of A-V rhythm cannot be detected by the patient or the physician. Sometimes, however, the patient may complain of giddiness, weakness, or palpitation, and the doctor may note an abrupt fall in the pulse rate. An explanation for these symptoms and signs has been given.

Should A-V rhythm be complicated by ventricular bigeminy, it is generally transitory, but it may be intermittent for months, the onset of bigeminy being partially determined by the length of the Q-P interval and by the site of origin of the ventricular contraction. It should be noted, however, that the critical Q-P interval, below which ventricular bigeminy ceases to appear, varies with the rate of the heart.

The prognosis for people with A-V rhythm is influenced and controlled by systemic disturbances and cardiac disease. The detection of the latter is sometimes possible by utilizing the following tests: vagal pressure, exercise, and atropine, provided such tests are performed and interpreted cautiously. These tests are only warranted when the ætiology of A-V rhythm is obscure. Six such cases have been reviewed. One proved to be due to organic disease and the others to vagal dysfunction. In the former there was no deterioration in health over a period of one year, although the disorder persisted for this period. In those people with abnormal vagal tone as the ætiological factor, it is probably possible to lead an active life for 25 years with intermittent A-V rhythm.

This study was carried out under the auspices of The Kirk Duncanson Research Fellowship in Medicine. Assistance and guidance was received from Dr. Rae Gilchrist who permitted me to make the observations upon his patients in The Royal Infirmary, Edinburgh. Expenses of the electrocardiographic records was covered by a grant from the Moray Endowment Fund. In conclusion, I would like to express my gratitude for all this assistance and to thank the nursing and technical staff for their co-operation.

REFERENCES

- Bain, V. W. C. (1939). *Lancet*, 1, 20.
 Barlow, P. (1927). *Ibid.*, 1, 65.
 Bishop (1921). *J. Amer. med. Ass.*, 77, 31.
 Blumgart, H. L., and Gargill, L. (1930). *Amer. Heart J.*, 5, 424.
 Bokspan, N. (1928). *Arch. Mal. Cœur*, 21, 802.
 Cowan, J., and Ritchie, W. T. (1935). *Diseases of the Heart*, 3rd ed., London, p. 85.
 — (1939). *Brit. Heart J.*, 1, 18-31.
 Cutts, F. B. (1937). *Amer. Heart J.*, 13, 451, and 14, 717.
 Dock, W. (1928). *Arch. intern. Med.*, 41, 745.
 Gallavardin, L., and Duma, A. (1920). *Arch. Mal. Cœur*, 13, 63.
 Goodman, M., and de Graff, A. C. (1930). *Amer. Heart J.*, 5, 375.
 Hewlett (1923). *Heart*, 10, 9.
 Jones, T. D., and White, P. D. (1927). *Amer. Heart J.*, 2, 266.
 Katz, L. N., and Kaplin, L. G. (1938). *Ibid.*, 16, 694.
 Kurtz, C. M., Bennet, J. H., and Shapiro, H. H. (1936). *J. Amer. med. Ass.*, 106, 434.
 Luten and Jensen (1932). *Amer. Heart J.*, 7, 593.
 Neslin, W., and Göttinger, I. (1932). *Deutsches Arch. Klin. Med.*, 173, 212.
 Reid, W. D. (1930). *Amer. Heart J.*, 5, 525.
 Resnik and Lathrop (1925). *Arch. intern. Med.*, 36, 229.
 Richardson (1922). *Ibid.*, 29, 253.
 Ritchie, W. T. (1923). *Edin. med. J.*, 2nd Series, 30, 621.
 Schotts, A. (1937). *Amer. Heart J.*, 13, 61.
 Sigler, L. H., Stein, I., and Nash, P. I. (1937). *Amer. J. med. Sci.*, 194, 356.
 Smith, C. S. (1921). *Ibid.*, 162, 575.
 Thomson, W. B. (1941). *Atrio-Ventricular Nodal Rhythm, Atrio-Ventricular Dissociation, and Reciprocal Rhythm*. M. D. Thesis, Edinburgh.
 Turner, K. B. (1931). *Amer. Heart J.*, 6, 743.
 Wedd, A. M. (1930). *Ibid.*, 5, 493.
 — (1941). *Amer. J. Dis. Child.*, 62, 154.
 Weiss, S., and Baker, J. P. (1933). *Medicine*, 12, 297.
 — and Ferris, E. B. (1934). *Arch. intern. Med.*, 54, 931.
 White, P. D. (1915). *Ibid.*, 16, 517.
 Williams, N. B., and James, H. (1913-14). *Heart*, 5, 109.
 Wilson, F. M. (1915). *Arch. intern. Med.*, 16, 86 and 989.
 Zeisler (1932). *Journ. Lab. Clin. Med.*, 18, 225.

MYOCARDIAL INFARCTION

BY

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Weigert (1880) was among the first to recognize infarction of the myocardium and to compare it with similar changes in other organs, for although in 1874 Hilton Fagge had described a series of cases of "fibroid disease" of the heart, which were probably myocardial infarcts, he considered them to be due to syphilis. Despite these observations it was not until some thirty years later that the condition began to attract the attention of clinicians. Herrick (1912) described the clinical features and Pardee (1920) discussed the electrocardiographic changes associated with its occurrence.

Any discussion of myocardial infarction should correlate the pathological changes with the anatomical structure of the heart. In this paper a review of the anatomy of the cardiac muscles and of the coronary arterial tree and the diseases thereof that may lead to muscle infarction is given. The consequences of interference with the blood flow in this tree are then discussed.

MUSCULATURE

It has been known for several centuries (Lower, 1669, and Gerdy, 1823) that the musculature of the mammalian cardiac ventricle does not form a homogeneous mass and can be dissected into several interlacing layers. In the present century (Mall, 1911; Flett, 1927; Robb, 1934; Lowe, 1939*a* and *b* and 1940; Robb and Robb, 1942) more detail has been added to the descriptions of the various layers of cardiac muscle in the ventricles, and it is now possible to recognize several muscles in the ventricular wall, which are in reality as distinct as the three glutei muscles making up the gluteal mass. The separation of these muscles was first shown by anatomical dissection, and has been confirmed by the demonstration of independent blood supplies and of their individual involvement in various pathological states (Lowe, 1940).

The musculature of the ventricles consists of two main parts. One, commencing superficially, spirals over the external surface of the heart and twists around itself at the apex of the ventricle (Fig. 1). It then passes upward to form the sub-intimal surface and papillary muscles of the left ventricle. It plays no part in the formation of the intimal surface of the right ventricle, but forms the full thickness of the muscle wall over the apical fourth of the left ventricle. Anatomically this muscle sheet can be divided into two halves, one arising from the sinus region, and the other from the bulbus region of the auriculo-ventricular ring. It is from these points of origin that the two halves take their names—*superficial sino-spiral* and *superficial bulbo-spiral* muscles.

The second main muscle mass (Fig. 2, 3, and 4) forms the deep layers and papillary muscles of the right ventricle, together with the portion of the left ventricle that lies between the pericardial and endocardial parts of the superficial sheet. In this deep mass are three separate muscles. One is confined to the wall of the left ventricle as a cylinder of spiralling fibres,

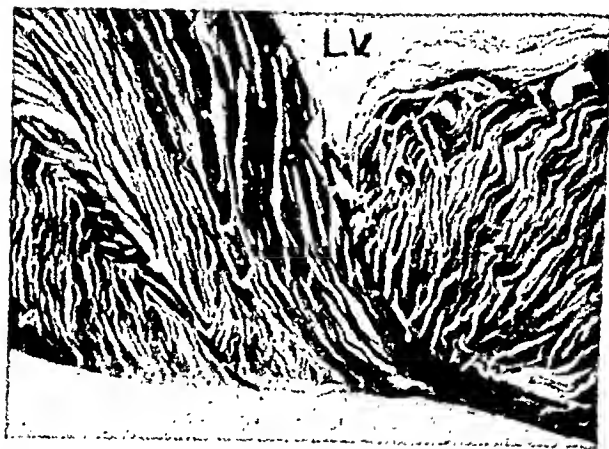


FIG. 1.—Photomicrograph of a longitudinal section through the apex of the left ventricle, L.V., illustrating the vortex formed by the two halves of the superficial muscle layer.

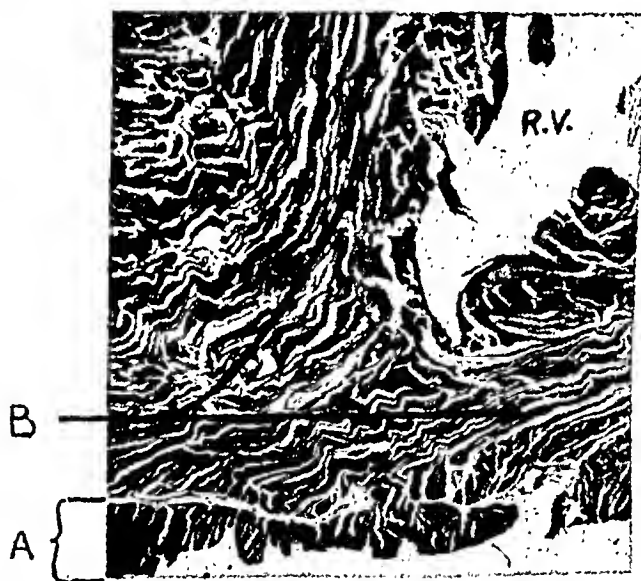


FIG. 2.—Section through the basal end of the interventricular septum showing the superficial muscle layer, (A), defined by a small artery, and the deep sino-spiral muscle, (B), splitting to enclose the right ventricle, R.V.



FIG. 3.—Section through the wall of the right ventricle to show the three muscle layers in contrast to the four layers in the left ventricle. (A) Superficial sino-spiral muscle. (B) Layer of deep muscle. (C) Endocardial portion of the deep sino-spiral muscle.

and is known from its site of attachment to the A-V ring as the *deep bulbo-spiral* muscle. The second can be recognized as a spiral sheet that surrounds the left ventricle and splits to enclose the right ventricle and form its innermost and chief muscle layer: the attachment of these fibres to the A-V ring is in the sinus region, and hence this muscle is known as the *deep sino-spiral*. The third encircles both ventricles in a spiral scroll manner, and is called the *scroll* muscle. These three deep muscles are confined to the upper three-quarters of the ventricular muscle mass.

Because of the spiral path of these muscles from base towards apex, it is often difficult to appreciate their independent existence in transverse sections. Unlike skeletal muscles, they are not separated by dense fascial sheets, but only by a small amount of loose connective

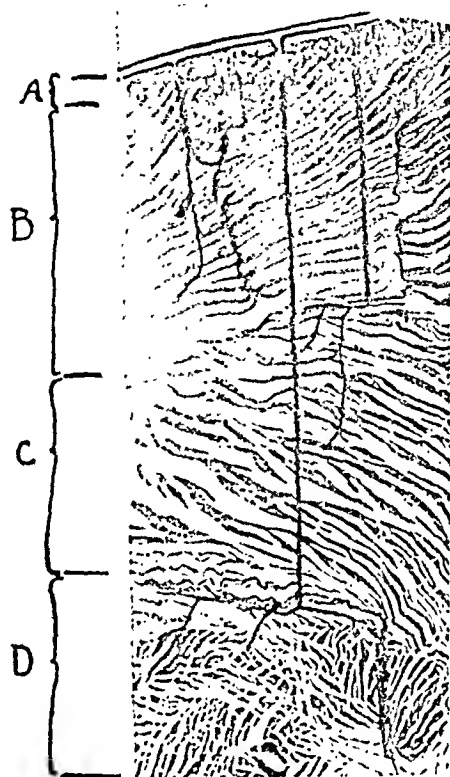


FIG. 4.—Section through the left ventricle near the base showing the four muscle layers. (A) Pericardial portion of superficial layer. (B) and (C) Two of the deep muscles. (D) Endocardial portion of the superficial layer. The peculiar arrangement of the muscular branches of the coronary arteries, by which the parent artery giving branches to the pericardial portion of a superficial muscle gives branches also to the endocardial portion of that muscle but not to the deep muscle in between, is indicated diagrammatically.

tissue. If a transverse section happens to be made in the plane of an artery, then the distinction between the bands may be quite obvious (Fig. 2).

The atrial (auricular) musculature likewise consists of two parts. The superficial consists of a sheet of muscle running transversely over both atria, a few fibres dipping into the inter-atrial septum. The deep comprises two sets of looped fibres each of which arises from the fibrous ring around the auriculo-ventricular orifice and passes antero-posteriorly around one or other atrium. In addition to these looped fibres, annular fibres surrounds the extremities of the large vessels, the auricular appendages, and the foramen ovale. As the superficial muscles are exceedingly thin, the atrial walls are composed almost entirely of the deep muscle bundles.

CORONARY ARTERIAL TREE

Arising from the sinuses of Valsalva in the aorta, the right and left coronary arteries branch and subdivide to be distributed over the surface of the auricles and ventricles, and later enter

their walls. Some branches lie between the muscle layers in connective tissue planes, whilst others pass at right angles to the surface to reach deeper layers of the wall before they give off branches which run parallel to the surface (Fig. 4). Although there is some overlap in distribution, the right auricle is supplied principally by two branches of the right coronary artery, and the left auricle derives its blood supply from the main left coronary artery and its circumflex branch.

Large anastomotic channels of arterial size between the major coronary branches are easily demonstrated in the hearts of aged people (Gross, 1921). These anastomoses exist at all ages (Lowe, 1937 and 1941), although physiologically they are of much less importance in childhood and youth, and therefore not easily shown by the methods of macroscopic anatomy. Their presence shows they normally carry blood, for if they did not they would disappear as do the umbilical arteries after section of the cord. Pressure difference between the ends of any vessel is the factor that determines the direction of blood flow in that vessel. In a normal coronary circulation arterial anastomoses will have approximately the same pressure at either end, so that the blood flow will be small and may easily change in direction from time to time. In hearts the seat of obstructive arterial changes, marked difference of pressure between the ends of the anastomotic channels can easily occur, and then these vessels enlarge and become visible to the naked eye. It must be remembered that a free anastomosis exists at all ages in all capillary beds.

A study of the traditional descriptions of the fields of supply of the major coronary arteries reveals no unanimity between authors as to the areas supplied. If the right and left coronary arteries are perfused with coloured gelatine solutions of similar viscosity to that of blood and under carefully controlled pressures, the following average description of these fields of supply in the ventricular walls can be demonstrated. The left coronary supplies all the left ventricle except the right third of the posterior wall, and the posterior third of the septum; in addition it supplies the left third of the anterior wall of the right ventricle. The right coronary supplies the anterior two-thirds of the septum and the right ventricle except the portion of the anterior wall just mentioned as being supplied by the left vessel; it also supplies that portion of the posterior wall of the left ventricle already mentioned. There is, however, considerable anatomical variation in the arteries of different hearts so that this description can only be regarded as approximate.

When occlusive arterial disease occurs, these distributions will be upset by opening up of the various arterial anastomoses described. It will then be impossible to predict the field of supply of any one of the major coronary branches.

By injection methods and careful dissection it is possible to show that small coronary branches within the walls supply portions of the various ventricular muscles, but owing to frequent anatomical variations it is of little value to try to determine which branches supply which individual muscle. It can also be shown that in the normal heart the smaller vessels supply one part of one muscle only.

It is of importance in any discussion on infarction to remember that the parent artery, which gives branches to the pericardial portion of a superficial muscle, gives branches also to the endocardial portion of that muscle but not to the deep muscles in between. This is due to the peculiar arrangement of vessels by which some branches penetrate through the thickness of the ventricular wall without giving branches to the muscles of the deep layer through which they pass (Fig. 4). Further, no one arterial branch supplies the whole of any one ventricular muscle.

DISEASES OF THE CORONARY ARTERIES

No essential difference exists between diseases of the arteries of the heart and those of other organs of the body, but because of the vital nature of the tissues concerned, coronary arterial disease often assumes great clinical importance. No matter which portion of the

coronary tree is affected, the gravity of the lesion is largely, if not wholly, determined by the degree of vascular obstruction. The commonest disease that produces vascular obstruction is undoubtedly arteriosclerosis,* which commonly affects the larger arteries in contrast to rheumatic fever, polyarteritis nodosa, and other inflammatory processes, which more often involve the small branches and arterioles.

ARTERIOSCLEROSIS

Many detailed studies have been made of the incidence of arteriosclerosis at different age periods and of its relationship to coronary artery obstruction (Kirch, 1930, and Wartman, 1933 and 1940), and they indicate that it is a process which is more severe in the latter half of life, although both early and advanced stages of the lesion may be seen in youth (Fig. 5).

The essential pathological change is in the intima, and is characterized by vascularization (Leary, 1935; Paterson, 1938; and Wartman, 1938), cellular infiltration, proliferative changes,



FIG. 5.



FIG. 6.

FIG. 5.—Section of descending ramus of the left coronary artery showing marked stenosing arteriosclerosis and recent thrombosis in an apparently healthy man of 23 years of age. In such cases it is not the mechanical block to the vessel that is important in causing death, but the rate of cessation of blood flow, and the state of the collateral circulation.

FIG. 6.—Macroscopic cross-sections of a stenosed femoral artery which have been cleared to show the vascularization, indicated by arrows, and hæmorrhage in the intima.

and deposition of lipoid, calcium, soaps, and other substances, often giving the appearance of an inflammatory reaction. The intima is greatly thickened at the site of the lesion and not infrequently this produces an appreciable diminution or even occlusion of the lumen. Secondary changes are also seen in the media which becomes thinned with the gradual replacement of muscle fibrous tissue.

Obstruction of the affected vessel may follow gradually by the growth of the intimal changes to such size as to prevent blood flow, or suddenly by thrombosis or hæmorrhage into the intimal (Fig. 6) or medial (Fig. 7) tissues. These hæmorrhages account for about 10 per cent of coronary artery obstructions (Wartman, 1940) and appear to be a sequel to the capillary vascularization of the wall (Moritz and Wartman, 1938; Wartman, Laipply, and Derr, 1943).

Intimal hæmorrhage may cause obstruction either by pushing forward the atheromatous

* The term arteriosclerosis is used in this paper as being synonymous with atherosclerosis, in accordance with the decision of the American Heart Association.



FIG. 7.—Section of a thrombosed popliteal artery to show hematomata (A) in the media. Weigert's and Van Gieson's stains.

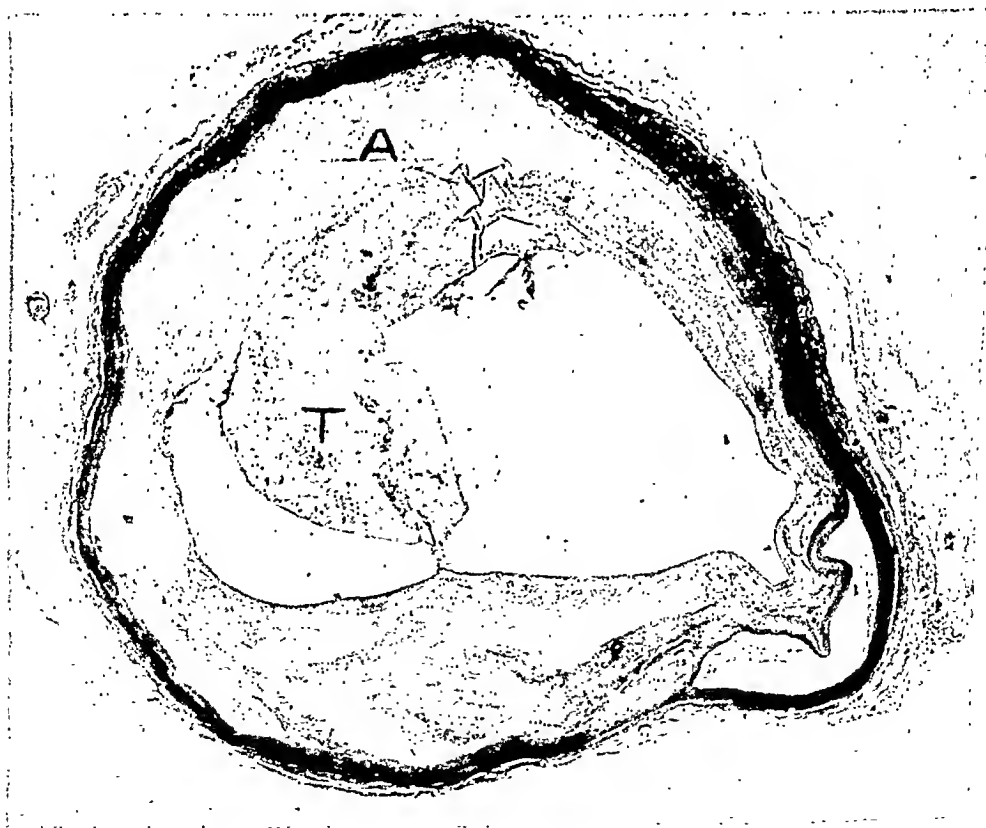


FIG. 8.—Section of femoral artery showing a thrombus (T) which has formed at the site of a large intimal hematoma (A). Weigert's and Van Gieson's stains.

plaque into the lumen of the vessel or by destruction of the endothelium, which is followed by thrombosis (Paterson, 1938; Wartman, 1938; Winternitz, Thomas, and Le Compte, 1938; Nelson, 1941) (Fig. 8). Occasionally these hæmorrhages are large (hæmatomata) (Fig. 6) and may bulge externally and even give rise to serious bleeding into the surrounding tissues.

Somewhat similar hæmorrhages are seen in dissecting aneurysms of the aorta, but there they are confined to the media. They frequently start as multiple foci which join and form a channel in the media of the aorta, and this channel may communicate either with the lumen of the vessel or rupture to the exterior. These have occasionally been recorded in the coronary arteries.

OTHER ARTERIAL DISEASES

Other conditions that are occasionally responsible for coronary artery occlusion are the acute and chronic inflammatory arterial diseases and also embolism. None of these are common causes but will be discussed briefly.

Acute Arteritis. This may occur during the course of any acute infectious disease or it may arise by the extension of a neighbouring inflammatory lesion or yet be mycotic in origin. Rare examples of so-called primary or idiopathic acute arteritis have been recorded (Karsner, 1937). Secondary thrombosis on the damaged site produces arterial blockage in these cases.

Polyarteritis Nodosa (Periarteritis nodosa). It has been estimated that some 70 per cent of cases of polyarteritis nodosa have involvement of the coronary arteries, and Grant (1940) has indicated that this disease is neither so rare nor so fatal as is generally thought. The histological picture seen in the affected vessels is that of an inflammatory response to some unknown agent. Polyarteritis nodosa usually attacks the small coronary arteries in scattered foci. Resulting infarcts are, therefore, small and disseminated (Fig. 9).

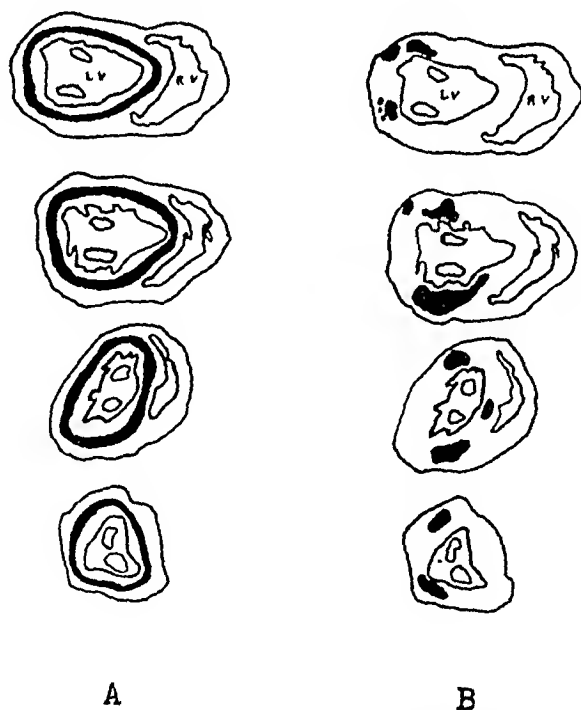


FIG. 9.—Comparison drawings of (A), the deep bulbo-spiral muscle and of (B), the multiple recent infarcts in the myocardium of a case of polyarteritis nodosa. Several small branch arteries were occluded and the infarcts were limited to the deep bulbo-spiral muscle.

Thrombo-Angiitis Obliterans. This is an occasional cause of coronary obstruction (Saphir, 1936), and consists of an inflammatory process in the vessel wall associated with thrombosis. A characteristic, although not universal, feature of the cellular response is the

presence of giant cells and infiltration with small round cells somewhat resembling a miliary tubercle.

Rheumatic Fever. In addition to producing a characteristic inflammatory lesion in the myocardium, this process also produces lesions in the walls of arteries. These are, however, rarely of clinical significance in comparison with the myocardial damage. Involvement of arterioles and small arterial branches is recorded (Karsner and Bayless, 1934) leading to occlusion with small scattered infarcts. Histological study of these vessels reveals no characteristic picture except for the occasional occurrence of Aschoff nodules. Holsti (1927) has recorded a peculiar verrucous endarteritis in which acidophilic material projects into the lumen of the affected vessels and closely resembles the vegetations seen on the cardiac valves.

Tuberculosis. Although tuberculous lesions of coronary arteries can be seen post-mortem (Goulcy, Bellet, and McMillan, 1933) in cases dead of tuberculosis, it is of little clinical significance as a cause of coronary obstruction. The arteries are involved either as part of a miliary spread or as a local extension of mediastinal or pericardial disease.

Syphilis. Coronary artery occlusion is a well-established, even if uncommon, sequel of syphilitic aortitis. Obstruction of the coronary vessels usually occurs at the ostia of the arteries in the sinuses of Valsalva, especially if this opening is abnormally high. It is due to thickening of the intima and scarring of the medial coat of the adjacent aortic wall, and occasionally leads to sudden death, for it is a main coronary vessel that is obstructed.

Embolism. One of the rarest forms of coronary obstruction is that due to embolism. The emboli may be fragments of cardiac vegetations or of tumours invading the blood stream. Fat droplets gaining access to the blood stream from bone injuries or gas bubbles entering the circulation through wounds of the neck may also form emboli. Fat embolism is the commonest of these conditions and can be recognized by "streak-like" hæmorrhages in the myocardium. Microscopically fat droplets can be demonstrated in small vessels by appropriate stains. As a cause of death following trauma it may easily be overlooked.

MYOCARDIAL ISCHÆMIA

A detailed account of the effects of myocardial ischæmia may now be given under the six following headings.

- (1) Infarction of the ventricular wall.
- (2) Interference with ventricular function.
- (3) Rupture of the ventricle.
- (4) Ventricular aneurysms.
- (5) Infarction of the auricular wall.
- (6) Electrocardiographic changes.

Infarction of the Ventricular Wall (Lowe, 1937, 1940, and 1941a). Failure to maintain an adequate blood supply to any part of the myocardium results in death of tissue. This may follow complete or even partial occlusion of one or more coronary branches. Sudden obstruction of a vessel will reduce the hydrostatic pressure distal to the block to a very low level, and create pressure differences across the ends of the anastomotic channels in that area, favouring the passage of blood towards the blocked vessel. If the anastomoses are sufficiently numerous and of sufficient size, they can maintain the circulation beyond the obstruction, and lack of blood supply to the tissue need not result. This, however, rarely happens, for in a normal circulation the sudden obstruction of an artery by an embolus produces spasm of the vessel immediately distal to the block and the flow of blood through these channels is rendered impossible. The immediate effect of sudden blockage of a vessel is therefore to deprive a section of tissue of its blood supply. This causes death of tissue unless it can survive until the spasm passes off. In general, the block will last long enough for death of the essential cells of the cardiac muscle to occur, but the interstitial cells of the fibrous tissue often survive. The size of the block of tissue involved will be determined by the size and situation of the vessel

obstructed, and may vary from a portion of one muscle bundle to portions of several muscles, even to the full thickness of the ventricular wall.

Partial obstruction of a vessel will lower the pressure in the artery beyond the block and again favour the passage of blood through the anastomotic channels. In contrast to complete occlusion there will be no spasm to interfere with the flow of blood into the vessel, beyond the partial obstruction. This results in the establishment gradually, and simultaneously with the developing block, of an adequate anastomotic circulation, so that the final sudden blocking of the partially occluded vessel will have a minimal effect. Thus complete obstruction may, gradually produced, effect no disturbance whatever in blood supply to the tissue. On the other hand, should the parent vessel supplying the anastomotic circulation become suddenly blocked, the area deprived of blood supply will be much greater than that following blockage of a similar vessel in a normal circulation.

If a gradual occlusion develops in several vessels at the same time, then the establishment of the collateral circulation will depend not only on the pressure differences across the ends of the anastomotic channels—this will determine only the direction of blood flow—but also on the volume of blood carried by the parent vessel of the anastomotic circulation. If this vessel is itself partially occluded it will be unable to carry the additional blood to supply the anastomotic circulation and may even fail to maintain an adequate circulation to its normal area of distribution. This will result in portions of heart muscle being deprived of blood supply without complete obstruction to any vessel. These areas will lie at the points farthest removed from their respective parent arteries and the muscle there will be replaced by isolated islands of scar tissues.

Embolism in a coronary artery of a young adult, presumably not the subject of arterial disease, will produce either rapid death or the development of an infarct in the ventricular wall. In general the effect so produced will be greater than it would be in an older person with an established anastomotic circulation.

The following types of infarction may be expected in the ventricular wall:

- (a) massive infarction, involving the whole thickness of the ventricular wall or parts of several muscles;
- (b) infarction confined to a portion of one muscle; and
- (c) scattered small islands of scar tissue.

(a) Massive infarction arises from the blockage of a main coronary artery in a normal circulation, or from the obstruction of an anastomotic channel carrying a large amount of blood in a system with occlusive arterial disease. This is exemplified by sudden obstruction of the anterior descending coronary artery—"the artery of sudden death."

Massive infarction may involve the full thickness of the ventricular wall or, if less extensive, portions of two or more muscles (Fig. 10 and 11). These infarcts are frequently wedge shaped with their bases externally. The exact explanation of this wedge shape is uncertain. However, similar wedges may be produced by injecting gelatine media into major coronary branches if improperly balanced pressures are used. It is probable, therefore, that the wedge results from disturbances in the dynamic balance of blood flow through the coronary tree.

(b) Infarction of a portion of a single muscle (Fig. 12, 13, and 14) is due to interference with the blood supply through a small arterial branch in the thickness of the ventricular wall. It is not the mechanical block to the vessel that is important, but the rate of cessation of blood flow and the state of the collateral circulation. Although infarction of any portion of a deep muscle has been observed, involvement of the pericardial portion of a superficial muscle is rarely seen.

(c) Patchy fibrosis, while it may follow any lesion that destroys muscle tissue in a disseminated, discrete fashion, may be caused by the gradual inability of the coronary circulation to carry enough blood to nourish the whole of the muscle mass. Therefore those parts most

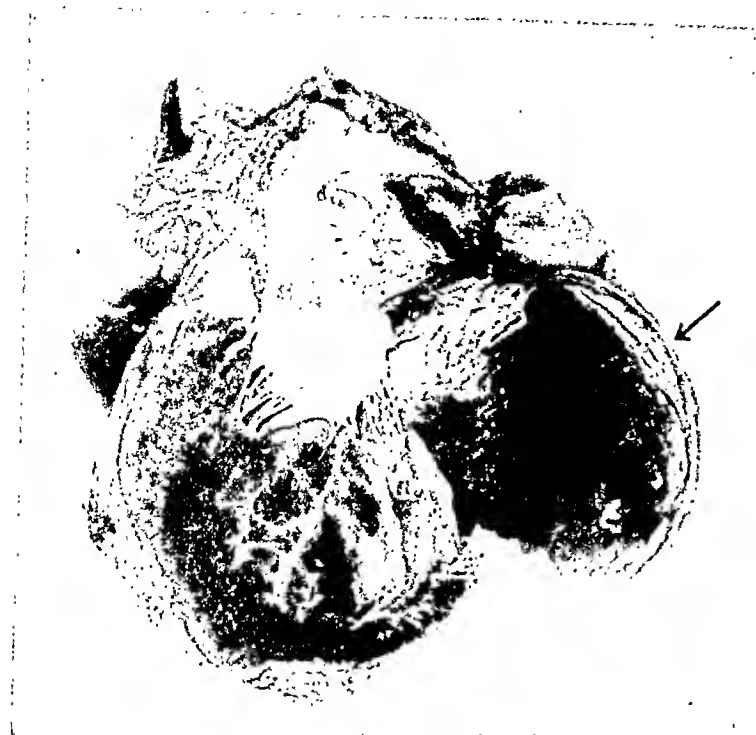


FIG. 10.

FIG. 10.—Aneurysm at the base of the left ventricle.

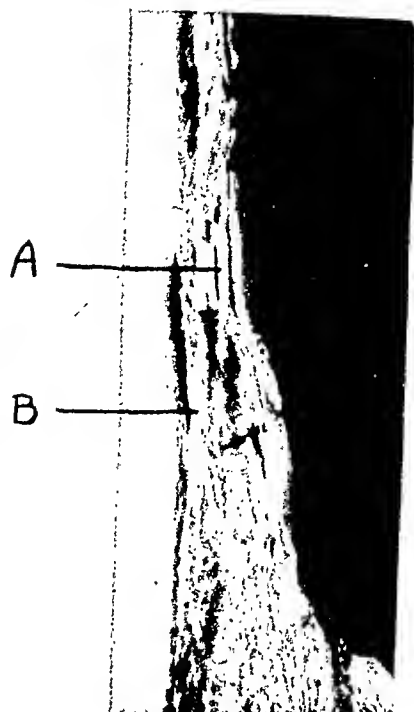


FIG. 11.

FIG. 11.—Wall of the aneurysm in Fig. 10 showing the two laminar scars at A and B.



FIG. 12.—Recent infarct involving the superficial muscles at the apex of the left ventricle and the lower end of the interventricular septum, with beginning aneurysm of the septum and mural thrombosis. Note the involvement of the papillary muscle, which is also composed of the superficial muscle bundles.

distant from the source of blood (aorta) will suffer most, i.e. small areas about the ends of arterioles which are supplied by the most obstructed channels.

Interference with Ventricular Function. Broadly speaking, interference with ventricular function can be considered under two headings.

(a) Interference with the ability adequately to expel blood. This depends on the amount of muscle tissue killed or damaged, and therefore ceasing to contribute to the force of cardiac



FIG. 13.

FIG. 13.—Aneurysm at the apex of the left ventricle showing a single laminar scar.



FIG. 14.

FIG. 14.—Wall of the aneurysmal sac in Fig. 13 showing the single laminar scar, A.

contraction. Following the sudden obstruction of a large vessel not previously constricted, there may be a gross drop in cardiac output and sudden death. If death does not result immediately, and if the damaged area is large enough, there will be a marked fall of systemic arterial blood pressure, and perhaps circulatory failure. This may end fatally, or a balance may occur and some of the anæmic muscle tissues recover, but the fall of blood pressure and circulatory failure that follow massive infarctions are likely to produce a vicious circle and lead to death in a few hours.

The quantity of blood flowing through a vessel is dependent on its lumen, and on the pressure difference across its ends. If the lumen is constant, as it is in many arteriosclerotic vessels, then the quantity of blood carried each minute is determined solely by the pressure differences. With the fall of systemic blood pressure following infarction of musculature, and the inability of rigid vessels to dilate, the area of muscle deprived of blood supply will increase, thus causing a further drop in systemic arterial pressure, and so establish a vicious circle. Frequently the damaged muscle is replaced by scar tissue and the resultant diminu-

tion of muscle means a reduction of ventricular power, manifested by a reduction in cardiac reserve (Lowe, 1941*b*).

The effects produced by the destruction of ventricular muscle depend both on the quantity of tissue destroyed and the particular muscle involved. The superficial muscles play a relatively unimportant part in the production of blood pressure (Robb and Robb, 1939), and destruction of portions of them may be unaccompanied by any circulatory change. By contrast, however, the deep muscles contribute the bulk of the ventricular power and involvement of one of them will produce marked disturbances.

(*b*) Rhythmic activity. If the infarcted tissue is in the interventricular septum, complete or partial heart block may follow. Damaged tissue at the margins of the infarct may act as an irritable focus and ventricular extrasystoles appear. Ventricular fibrillation sometimes develops, and is usually fatal as it is followed by failure of co-ordinated ventricular contraction.

Ventricular Rupture. Rupture of a ventricle may follow destruction of muscle in its wall. If an infarct involves the full thickness of the wall, then tearing of the dead muscle fibres occurs as soon as young granulation tissue appears and the muscle commences to break up. If only portion of the thickness of the wall is involved rupture occurs only occasionally. In such cases hæmorrhage from a large vessel in the damaged area, or communication with the ventricular cavity may allow blood to enter the muscle planes and so dissect a path to the pericardial cavity (Lowe, 1940). Bleeding into the pericardial cavity occurs and death results from pericardial tamponade.

These events usually follow within ten days of the arterial occlusion; after that time the scar tissue replacing the muscle seems strong enough to withstand the tensions developed in the wall, and although it may gradually stretch, it does not give way suddenly.

Aneurysm of the Ventricle. Weakening of the ventricular wall follows replacement of muscle by the inelastic collagen fibres of scar tissue, and the consequences of this are determined by the muscle involved. There may be merely a thinning of the wall or aneurysm formation. Ventricular aneurysms are of two types; basal (Fig. 10) and apical (Fig. 13).

At the apex of the left ventricle the wall is formed by the two layers of superficial muscle and involvement of the superficial musculature at the apex leads to thinning of the wall with the development of a laminar scar. However, if almost the full thickness of the wall is affected an aneurysm will develop (Fig. 13).

As there are several muscle layers near the base of the ventricles, the superficial muscles are unimportant in the production of thinning or aneurysm formation. A study of laminar scars (Lowe, 1941*c*) shows that involvement of a single deep muscle results in thinning of the wall without bulging. The presence of at least two laminar scars in the wall of basal aneurysms of the ventricle indicates that destruction of two deep muscle layers is essential to their formation (Fig. 11).

The physical basis of aneurysm formation is the same in both ventricle and aorta. In both places muscle tissue is active in withstanding pressure, and when enough of it is destroyed and replaced by collagen, gradual stretching and sac formation occurs.

Endocardial thrombosis (Fig. 12) is usually associated with massive infarction or an aneurysmal sac. It is rarely seen when the inner portion of a superficial muscle alone is involved because there is usually no endocardial damage as a thin layer of muscle between endocardium and infarcted tissue frequently survives, possibly deriving its nourishment directly from the ventricular cavity. Emboli may arise from these endocardial thrombi and produce infarction in any viscus as a sequel to myocardial infarction.

*Infarction of Cardiac Auricles.** The principles outlined in discussing ventricular infarcts are strictly applicable to those occurring in the walls of the auricles. In one reported series

* As the term "auricle" is by custom used in clinical and electrocardiographic terminology, it has been retained in place of "atrium" and refers to the whole chamber and not merely to the appendage.

of post-mortem examinations, auricular infarcts were seen 31 times in 182 (17 per cent) cases of ventricular infarction (Cushing, Feil, Stanton, and Wartman, 1942). Most of them were in the right auricle and involved the appendage more often than other parts of the chamber. Endocardial thrombosis was common in these instances and was due to the frequent involvement of the deep muscles of the auricle, which form the bulk of the auricular wall.

Electrocardiographic Changes. Following myocardial infarction electrocardiographic changes occur but their interpretation is difficult (Lowe, 1941a). The origin of the cardiac potentials is uncertain, but if, as seems probable, they are produced by the spread of the "impulse" along muscle bundles, and not by a current of action, then until the route of spread of that impulse is known definitely, any interpretation of changes following infarction must be empirical. When muscle is damaged the route of impulse spread is presumably disturbed and the cardiographic tracing will change from the normal, and such a change is likely to be permanent. In addition to this change in route, there will be a current of injury superimposed on the record, but this current is only transitory, and varies from hour to hour, finally disappearing. Non-fatal infarcts rarely involve a very large amount of any one muscle and the permanent disturbance of the electrocardiographic record is often small, whereas the immediate change is often gross.

Attempts to localize the site of infarction by cardiographic tracings must be based on both empirical observations and the anatomical structure of the heart. Most of the investigations so far recorded have considered massive infarctions involving several muscles at various positions in the ventricular wall. There are well-recognized tracings associated with anterior apical and posterior basal infarctions. However, some success has been achieved recently in recognizing tracings corresponding to involvement of single muscle bundles. At present it seems unlikely that any further localization than this is possible, because experimental observations indicate that an injury anywhere along the course of a single muscle produces the same electrocardiographic disturbance.

The disturbances in rhythmic activity of the ventricular muscle are also reflected in the cardiograph as ventricular extrasystoles, heart block, or even terminally as ventricular fibrillation.

Abnormalities in the auricular complex of the cardiogram are present in many cases of auricular infarction. These indicate variations in either the rhythmical activity or disturbance in the path of the impulse through the auricular wall. The former is represented by extrasystoles, fibrillation, wandering pacemaker, or nodal rhythm, and the latter by depression of the P-Q interval ("cupule").

Both in a carefully studied series of human cases (Cushing *et al.*, 1942) and in animal experiments no one of these disturbances was present in every case. Any disturbance in auricular electrical activity may therefore suggest auricular muscle damage—possibly due to infarction.

To conclude this essay we may indicate the directions in which these studies should aid the clinician now and in the future. It will be readily appreciated from the foregoing account of the structure and function of the heart that many of the indications of the existence of a myocardial infarct have a ready explanation. Fall of arterial blood pressure is in most cases due either to the amount of muscle tissue destroyed or to the particular muscle involved. Abnormalities in cardiac rhythm and the electrocardiographic changes will be better understood when sufficient data have been compiled relating to the problems of the electrical activity of the heart. Accurate localization of the specific muscle bundles involved may enable us to predict when rupture of the ventricles or even when congestive cardiac failure is to be expected.

The prognosis of a case of myocardial infarction depends as much upon the disease

causing the arterial block as it does upon the extent of the muscle damage. This factor determines the size of the infarct that follows the obstruction of any given vessel and whether or not a recurrence of the episode is to be expected. The varying condition of the coronary arteries is probably the cause of the great variation in the expectation of life after myocardial infarction—a variation from a few moments to some fifteen years.

A knowledge of the behaviour of diseased coronary vessels is essential in discussing the surgical procedures advocated for improving the myocardial blood supply in coronary artery disease. These procedures aim at establishing new anastomotic channels between extra-cardiac and cardiac arteries by placing intercostal muscles or omentum in contact with the pericardium. It is assumed in these procedures that the arterial pressure gradient will force blood from the extracardiac to the cardiac vessels. There is however no guarantee that such a gradient will exist. In those cases generally suitable for operative interference the one deficient in blood supply will frequently be deep in the ventricular wall. It is then very doubtful if a satisfactory pressure gradient will exist to transfer any quantity of blood to the heart, and it is possible that the flow will be in the opposite direction. This unpredictable factor probably causes the very variable results that follow these surgical procedures.

REFERENCES

- Cushing, E. H., Feil, H. S., Stanton, E. J., and Wartman, W. B. (1942). *Brit. Heart J.*, 4, 17.
 Fagge, C. H. (1873). *Trans. Path. Soc. London*, 25, 64.
 Flet, R. L. (1927). *J. Anat.*, 62, 439.
 Gerdy (1823). *Recherches, Discussion et Propositions*, Paris (quoted by Cloquet, J., 1828. *Anatomie de l'Homme*, Paris, 3, 500).
 Gouley, B. A., Bellet, S., and McMillan, T. M. (1933). *Arch. intern. Med.*, 51, 244.
 Grant, R. T. (1940). *Clin. Sci.*, 4, 245.
 Gross, L. (1921). *Blood Supply to the Heart*, Oxford Med. Pub.
 Herrick, J. B. (1912). *Trans. Ass. Amer. Physicians*, 27, 100.
 Holsti, O. (1927). *Arb. path. Inst. Zu. Helsingfors*, 5, 110.
 Karsner, H. T. (1937). *Ann. intern. Med.*, 11, 164.
 Karsner, H. T., and Bayless, F. (1934). *Amer. Heart J.*, 9, 557.
 Kirch, E. (1930). *Ergebn. allg. Path. path. Anat.*, 23, 427.
 Leary, T. (1935). *Amer. Heart J.*, 10, 328.
 Lowe, T. E. (1937). *Roy. Melbourne Hosp. Clin. Rep.*, 8, 79.
 — (1939a). *J. Path. and Bact.*, 49, 195.
 — (1939b). *Med. J. Australia*, 2, 491.
 — (1940). *Ibid.*, 1, 826.
 — (1941a). *Ibid.*, 1, 693.
 — (1941b). *Ibid.*, 2, 447.
 — (1941c). *Amer. Heart J.*, 21, 326.
 Lower, R. (1669). *Tractus de Corde* (quoted in *Quain's Anatomy*, 4, 13, and 73, 1929).
 Mall, F. P. (1911). *Amer. J. Anat.*, 11, 211.
 Moritz, A. R., and Wartman, W. B. (1938). *Amer. J. med. Sci.*, 195, 65.
 Nelson, M. G. (1941). *J. Path. and Bact.*, 53, 105.
 Pardee, H. E. B. (1920). *Arch. intern. Med.*, 26, 244.
 Paterson, J. C. (1938). *Arch. Path.*, 25, 474.
 Robb, J. S. (1934). *Med. and Professional Women's J.* March.
 Robb, J. S., and Robb, R. C. (1939). *Amer. J. med. Sci.*, 197, 7.
 — (1942). *Amer. Heart J.*, 23, 455.
 Saphir, O. (1936). *Ibid.*, 12, 521.
 Wartman, W. B. (1940). *Amer. J. med. Sci.*, 186, 27.
 — (1938). *Amer. Heart J.*, 15, 459.
 — (1940). *Amer. Assc. Sci.*, publication, 13, 122.
 Wartman, W. B., Laipply, T. E., and Derr, W. (1943). Unpublished experiments.
 Weigert, T. (1880). *Virchows Arch.*, 79, 87.
 Winternitz, M. C., Thomas, R. M., and Le Compte, P. M. (1938). *The Biology of Arteriosclerosis*, Springfield, Thomas.

ACUTE LEFT AURICULAR FAILURE

BY

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Various hypotheses have been advanced to account for the occurrence of acute pulmonary œdema in association with mitral stenosis during pregnancy, but none is entirely satisfactory. The following two cases are recorded because they present certain clinical and pathological features that may help to throw some light on the subject.

CASE RECORDS

Case 1, M. H. H. A primigravida, aged 37, was admitted to hospital, in the fifth month of pregnancy, on account of recurrent attacks of acute dyspnœa with hæmoptysis.

She gave a history of rheumatic fever at the age of seven but, apart from slight shortness of breath on exertion, had been free from symptoms until the third month of pregnancy when she became increasingly dyspnœic and developed a persistent cough with blood-streaked sputum. Two months later she had a sudden acute attack of dyspnœa at rest and coughed up a moderate amount of bright red blood. Three further attacks occurred during the next three days and she was admitted to St. Mary's Hospital, Manchester, under the care of Dr. J. W. A. Hunter, very collapsed, extremely dyspnœic, and coughing up considerable quantities of pink frothy sputum. The radial pulse was only just palpable and there was a trace of œdema at the ankles. Moist sounds were present all over the chest. The blood pressure was 100/70. The clinical picture was that of acute left-sided heart failure. Under treatment her condition improved rapidly and next morning there were only scattered moist sounds in the chest with slight hæmoptysis; the œdema had disappeared and there was no systemic venous engorgement. The heart was grossly enlarged, but its rhythm was regular, and there was a loud apical presystolic but no other diastolic murmur.

With rest in bed her condition steadily improved, the dyspnœa subsided, and the hæmoptysis ceased in a few days. She remained well for two weeks, but then, without apparent cause, became acutely dyspnœic and coughed up a considerable quantity of blood. The suddenness of this relapse suggested the possibility of a pulmonary embolus. She failed to respond to treatment, developed severe pulmonary œdema, and died in a few hours.

Autopsy was performed by Dr. F. A. Langley. The lungs were grossly œdematous, but there was no sign of recent pulmonary embolism, nor of old infarction. The heart weighed 400 g. There was a button-hole stenosis of the mitral valve, measuring 15×3 mm. The aortic valve was slightly scarred and the cusps were adherent for a short distance from their bases. The pulmonary and tricuspid valves were healthy. The left auricle was considerably dilated and hypertrophied, its wall being 4 mm. thick. The right ventricle also was considerably hypertrophied, the wall being 9 mm. thick. The pulmonary arteries were moderately atheromatous. Apart from some cortical congestion the kidneys were normal.

The estimated age of the fœtus was 6½ months.

Case 2, M. McA. A primigravida, aged 34, was first seen in September 1941 when 4½ months pregnant. She gave no history of rheumatic fever, but had had occasional swelling of the ankles since the age of 15. She had been somewhat breathless on exertion for several years, and more so during pregnancy. On examination there was a coarse apical presystolic thrill, accompanied by a loud crescendo murmur. Moist sounds were present at the base of the lungs, but there was no evidence of right ventricular failure.

A cardiogram showed slight right axis deviation with sinus rhythm. Tele-radiograms showed some enlargement of the pulmonary conus, moderate enlargement of the left auricle, and considerably increased vascular markings in the lungs. A therapeutic abortion was performed at St. Mary's Hospital and she was advised to have no more children.

A year later she was re-admitted to St. Mary's Hospital under the care of Dr. J. W. A. Hunter, as

an urgency, $4\frac{1}{2}$ months pregnant, with right ventricular failure, considerable œdema, and an enlarged tender liver. When seen by one of us (A. M. J.) five days later, the œdema had subsided and the venous engorgement had greatly lessened, but she was still very dyspnoic. The heart rhythm was regular, and there was a coarse apical presystolic thrill accompanied by an exceptionally loud and harsh crescendo murmur. Termination of pregnancy was advised when her condition had improved. Three weeks later she was given $\frac{1}{3}$ of a grain of omnopon and $\frac{1}{150}$ of a grain of scopolamine prior to therapeutic abortion, and collapsed with very slow respiration. Severe right ventricular failure with gross œdema rapidly developed. When her condition had improved somewhat she was transferred to the Manchester Royal Infirmary (September 30). She was then only slightly dyspnoic at rest, but had œdema up to the groins and in the hands, with free fluid in the abdomen. The percussion note was impaired and there were moist sounds at the bases of the lungs. The blood pressure was 115/75. A cardiogram showed an increased degree of right axis deviation compared with her previous record. Under treatment she improved slowly, but on October 6 she was again given $\frac{1}{4}$ of a grain of morphia, and about an hour later became extremely dyspnoic and almost pulseless. With theophylline-ethylene-diamine and atropine she slowly improved, but two days later she aborted. Following abortion her general condition improved rapidly, but she still had extensive œdema and the liver border was two inches below the umbilicus. A few days later the œdema and venous congestion had considerably lessened but her cough had increased and moist sounds were heard in the chest. At the same time she began to have attacks of paroxysmal dyspnoea lasting several hours. On October 20 at 6 a.m. she suddenly became intensely dyspnoic, moist sounds were audible over the whole chest, and she coughed up considerable amounts of frothy sputum. She was pulseless and very cyanosed. With oxygen, atropine, and intramuscular theophylline-ethylene-diamine she improved temporarily but then relapsed and died at 10.40 a.m.

Autopsy was performed by Dr. W. Susman, 24 hours after death. The lungs were œdematous and the right pleura contained about a litre of clear fluid. There was passive congestion of all organs. The heart weighed 260 g.; the right ventricle was considerably hypertrophied, and the left auricle was dilated and greatly hypertrophied. The mitral valve exhibited a severe degree of stenosis, the orifice measuring 5 mm. \times 10 mm.; there were small recent rheumatic vegetations on the valve. The aortic valve was healthy but the thoracic aorta showed two patches about 2 cm. in diameter of a pearly grey colour with numerous longitudinal puckerings—appearances suggestive of a rheumatic aortitis. The pulmonary arteries exhibited considerable atheroma. Apart from slight scarring of the capsular surfaces and severe passive congestion the kidneys appeared healthy. The uterus was enlarged (8 \times 10 \times 3.5 cm.) and the cavity was filled with adherent thrombus.

Histological examination showed diffuse fibrosis of the auricular muscle, and a patchy, mainly perivascular, fibrosis of both ventricles, more severe on the left. The appearances of the aortic lesions were typical of rheumatic aortitis.

DISCUSSION

In 1872 Peter described a typical severe attack of pulmonary œdema occurring during the fifth month of pregnancy from which recovery occurred following venesection and emetics, but which recurred at the same stage of a subsequent pregnancy when he was able to detect characteristic signs of mitral stenosis with a presystolic murmur. His description makes it clear that normal rhythm was present, and in a detailed account of the auscultatory findings he makes no mention of any other diastolic murmur. Thus, in the stage of pregnancy, the presence of normal rhythm, and of a murmur confined to auricular systole, Peter's case resembles those we have described. Subsequently cases were described by several workers, mostly in France and in America (Jensen, 1938).

Two main hypotheses have been put forward to account for the development of acute pulmonary œdema in pregnancy—the "toxic" and the "mechanical." Vinay (1896) described pulmonary œdema in a pregnant woman with chronic nephritis but no heart disease, and a second case, fatal in the fifth month of pregnancy, in a woman with heart disease and albuminuria, which he attributed to renal damage. Pouliot (1904) collected reported cases of pulmonary œdema and found that renal damage was present in many of them. The view generally accepted seems to have been that of Schellong (quoted by Laennec, 1930) that as pulmonary œdema could not be mechanical it must be "toxic." There now appears to be little satisfactory evidence to support the toxic hypothesis, and even in cases of renal disease with hypertension, pulmonary œdema is usually ascribed to left ventricular failure. In our cases, however, there was no hypertension during life and no evidence of renal disease at autopsy.

In left ventricular failure there is no clear dividing line between pulmonary congestion and acute pulmonary œdema; similarly, in mitral stenosis pulmonary congestion and its rarer sequel, acute pulmonary œdema, differ only in degree and are produced by the same mechanism. That mechanism may now be considered.

From his experimental observations on the dynamics of the circulation Wiggers (1923) showed that, under normal conditions, ventricular diastole may be divided into three phases (Fig. 1, A):

(a) In *early diastole*, when the mitral valve first opens, the blood flows rapidly from the auricle into the empty ventricle.

AURICULAR PRESSURE AND VENTRICULAR FILLING IN MITRAL STENOSIS

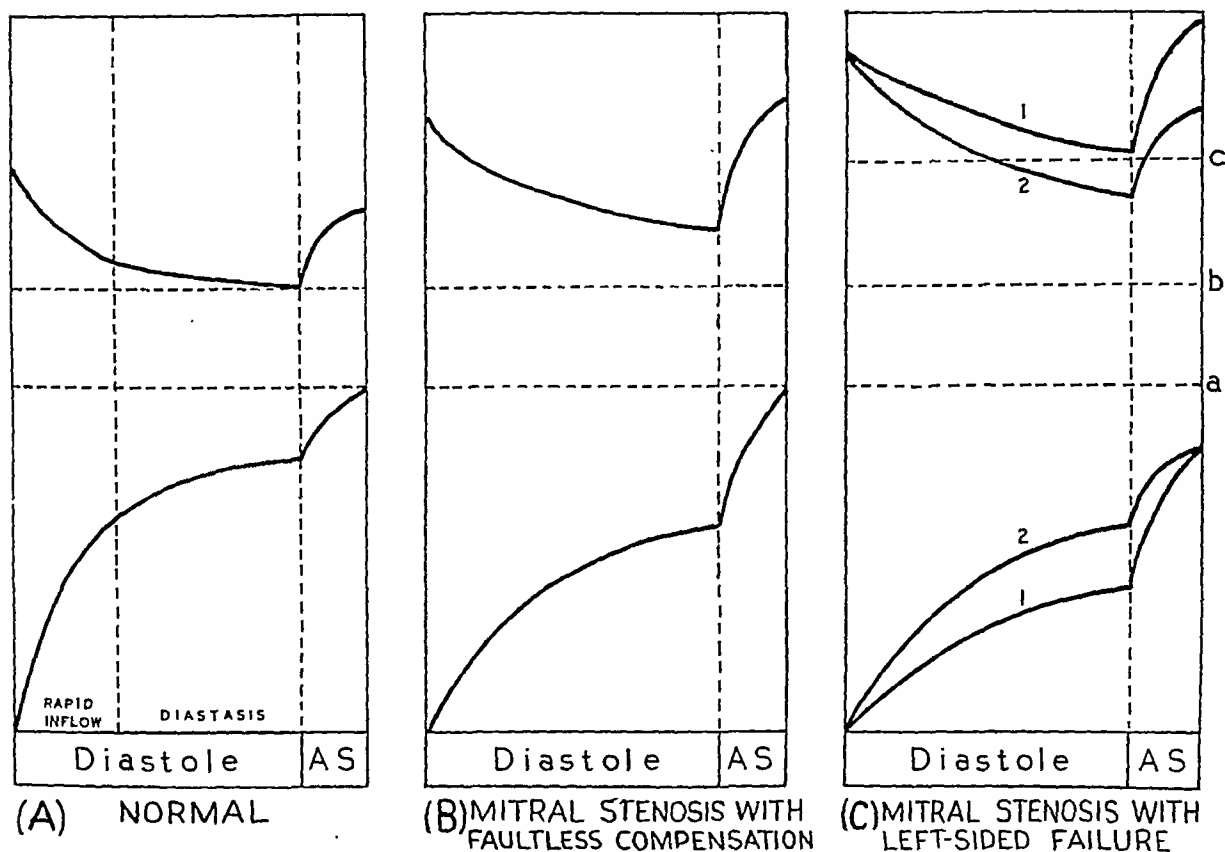


FIG. 1.—The upper curves represent diagrammatically the auricular pressure and the lower curves the ventricular volume during diastole and auricular systole (AS).

a is the volume of the ventricle when filling is complete;

b is the normal auricular diastolic pressure at the onset of auricular systole ;

c is the level of auricular diastolic pressure (and of pulmonary venous pressure) which would lead to a rise of pulmonary arterial blood pressure.

(A) represents the normal course of events during diastole when the heart rate is slow. During the period of rapid inflow the ventricular volume rapidly increases and the auricular pressure falls correspondingly. During diastasis there is comparatively little ventricular filling. At the onset of auricular systole the ventricle is already almost full, so that the auricle plays only a small part in ventricular filling.

(B) represents the events during diastole when faultlessly compensated mitral stenosis is present. Owing to the obstruction to ventricular filling the ventricular volume rises more slowly and the auricular pressure falls correspondingly slowly. At the onset of auricular systole the ventricle is far from full and the auricular diastolic pressure higher than normal. For both these reasons auricular systole makes an abnormally large contribution to ventricular filling.

(C) represents the events when left ventricular filling is no longer maintained ("left-sided failure").

1 shows how an increased obstruction at the mitral valve causes slower ventricular filling, and an auricular contribution equal to that in (B) fails to bring ventricular filling to normal ;

2 shows how the same result occurs when the auricle fails to supply its quota, the mitral stenosis remaining unchanged.

In these circumstances the elevation of the auricular diastolic pressure (and pulmonary venous pressure) above *c* would lead to pulmonary arterial hypertension and right ventricular hypertrophy.

(b) In *mid-diastole*, when the initial difference in pressure between auricle and ventricle has been relieved, the blood current is much more sluggish. To this phase he gave the name "diastasis."

(c) In *presystole*, when the auricle contracts, the rate of blood flow is again increased.

When the mitral orifice is stenosed, it takes longer to equalize the pressures in auricle and ventricle; consequently the rate of ventricular filling during early and mid-diastole becomes more uniform.

When stenosis is severe the pressure in the auricle remains considerably higher than that in the ventricle throughout early and mid-diastole, and when auricular systole supervenes the auricular wall is still under considerable tension. This, in accordance with Starling's (1918) law, evokes a more powerful auricular contraction, and the dilated auricle develops a compensatory hypertrophy.

As the auricular diastolic pressure rises the pulmonary pressure rises with it, first on the venous side, leading to congestion in the lungs, and later on the arterial side, so that the burden is thrown back upon the right ventricle.

Fishberg (1940) has accordingly described the evolution of mitral stenosis in three stages (Fig. 1, B and C):

- (1) *A stage of faultless compensation* dependent on prolongation of the phase of "rapid inflow" at the expense of "diastasis," and auricular hypertrophy.
- (2) *A stage of failure of the left side * of the heart* with pulmonary engorgement, a rise of pulmonary arterial pressure, and hypertrophy of the right ventricle.
- (3) *A stage of failure of the right side of the heart* with systemic venous engorgement.

A case will pass from the first to the second stage if the valvular stenosis increases, or if the compensatory mechanisms break down owing to a weakening of auricular systole or to the onset of auricular fibrillation (Fig. 1, C (1 and 2)). In either event, ventricular filling can only be maintained by an increase of the auricular diastolic pressure. This increase in pressure is transmitted to the pulmonary veins, producing chronic pulmonary congestion and perhaps hæmoptysis. It is usual for the signs of pulmonary congestion to develop gradually, as the slowly increasing stenosis leads to gradual left auricular failure.

In both our cases, however, pulmonary congestion developed suddenly and led to acute pulmonary œdema. A sudden increase of pulmonary venous pressure may be due either to a sudden increase in mitral obstruction or to acute left auricular failure. The former might occur if the mitral valve were suddenly occluded by a ball thrombus, but in our cases no auricular thrombus was present at autopsy.

The possibility of sudden left auricular failure being responsible for the development of acute pulmonary œdema in cases of mitral stenosis depends on the extent to which auricular systole contributes to ventricular filling. Kerkhof's (1936) observations on the cardiac output in mitral stenosis with auricular fibrillation, before and after the restoration of sinus rhythm with quinidine, led him to conclude that auricular contraction was responsible for about 25 per cent of ventricular filling, but in these experiments he made no allowance for the rise in the auricular diastolic pressure associated with fibrillation,† which is an important factor in maintaining ventricular filling. Further, fibrillation is more likely to occur in auricles that have been severely damaged by the original rheumatic infection, and his experiment, therefore, fails to give a true measure of the effect of systole in the more healthy auricle that has never fibrillated. For these two reasons it seems probable that Kerkhof's estimate of the part played by auricular systole is unduly conservative.

This is confirmed by Wiggers and Katz' (1922) observations on the varying contribution of the auricle to ventricular filling at different heart rates. When diastole is prolonged the ventricle is already almost full when the auricle contracts; in these circumstances, auricular

* Presumably Fishberg referred to failure of the left *auricle* since, in mitral stenosis, failure of the left side of the heart could not be due to ventricular failure.

† Unpublished personal observations in experimental fibrillation.

systole accounts for only 10 per cent of ventricular filling. When, however, the heart is beating rapidly, and diastole is short, the auricle contracts when the ventricle is only partially filled; in these circumstances 50–60 per cent of ventricular filling may be due to auricular systole. The effect of mitral stenosis is comparable to that of tachycardia; owing to the reduced rate of blood flow through the mitral valve, ventricular filling is far from complete at the onset of auricular systole, so that auricular contraction becomes correspondingly more important in maintaining ventricular filling.

In our two cases the severe degree of stenosis found at autopsy, coupled with the fact that during life the murmur was confined to pre-systole, suggests that the amount of blood passing through the mitral orifice during early diastole was insufficient to produce a murmur. If this be true, ventricular filling in such cases would be largely dependent on auricular systole. In order to maintain ventricular filling under these circumstances auricular systole must be powerful, and in both our cases the wall of the left auricle was greatly hypertrophied.

In severe mitral stenosis, when ventricular filling is largely dependent on auricular systole, if sudden failure of the auricle occurs, ventricular filling will then depend solely upon an auricular diastolic pressure previously inadequate to effect any substantial filling. Adequate filling can only be re-established if the auricular diastolic pressure rises rapidly. If this occurs, it will lead to a corresponding rise of pulmonary venous pressure, with sudden pulmonary congestion and ultimately acute pulmonary œdema (*Case 1*).

Gerhardt (quoted by Fishberg, 1940) showed in animal experiments that if the pulmonary venous pressure rose above 7 cm. of water the pulmonary arterial pressure began to rise. Thus if the sudden rise of pulmonary venous pressure reaches a sufficiently high level, a sudden rise of pulmonary arterial pressure will follow, and this may lead to acute right ventricular failure (*Case 2*).

The combination of severe mitral stenosis with an efficient auricle is only likely to occur if the original rheumatic infection is associated with severe mitral endocarditis but comparatively little auricular myocarditis, and the infrequency of this combination may account for the comparative rarity of the syndrome. In the majority of cases, acute rheumatic carditis leads to a moderate degree of mitral stenosis coupled with a correspondingly severe lesion of the auricular myocardium, which predisposes to auricular fibrillation. In that case a moderately raised auricular pressure may be sufficient to maintain ventricular filling but if ventricular filling is to be maintained as the stenosis increases, the auricular pressure must continue to rise, so leading to gradually increasing pulmonary congestion. In Table I we have endeavoured to compare the sequence of events in chronic and acute left auricular failure.

TABLE I
LEFT AURICULAR FAILURE

| | Chronic | | | | | Acute | | |
|--------------------------------|------------------------|---|--|--|--|-------------|---|---|
| Mitral endocarditis | + | + | | | | + | + | + |
| Left auricular myocarditis .. | + | + | | | | | + | |
| Mitral stenosis | + | + | | | | + | + | + |
| Left auricular hypertrophy .. | | + | | | | + | + | + |
| Rhythm | Auricular fibrillation | | | | | Normal | | |
| Left auricular failure | Chronic | | | | | Acute | | |
| Lungs | Chronic congestion | | | | | Acute œdema | | |

Both our patients died in mid-pregnancy and it seems probable that the increasing blood volume and rising heart output at this stage of pregnancy were factors in precipitating heart failure.

SUMMARY

Two cases of mitral stenosis with acute pulmonary œdema leading to death about the middle stage of pregnancy are described.

The mechanism of production of this complication is discussed and it is attributed to acute left auricular failure.

We are indebted to Professor S. L. Baker for the pathological work, which was carried out in his Department.

REFERENCES

- Fishberg, A. M. (1940) *Heart Failure*, London, p. 502.
Jensen, J. (1938). *The Heart in Pregnancy*, St. Louis, p. 226.
Kerkhof, A. C. (1936). *Amer. Heart J.*, **11**, 206.
Laennec, Th. (1930). *Cardiopathies mitrales et gestation*, These, Paris.
Peter, M. (1872). *L'Union Medicale*, **13**, 278.
Pouliot, L. (1904). Quoted by Jensen (1938).
Starling, E. H. (1918). *The Law of the Heart*, Linacre Lecture, London.
Vinay, C. (1896). *Lyon. Med.*, **83**, 289.
Wiggers, C. J. (1923). *Circulation in Health and Disease*, Philadelphia, p. 99.
Wiggers, C. J., and Katz, L. N. (1922). *Amer. J. Physiol.*, **58**, 439.

CARDIAC INVOLVEMENT IN SPIROCHÆTAL JAUNDICE

BY

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There are relatively few published articles on the cardiac complications of spirochætal jaundice. Our purpose is to review briefly the available papers dealing with spirochætal jaundice complicated by cardiac disturbances, and to report a case.

REPORTED CASES

Clinical material. Garnier and Reilly (1916) described a case in which an aortic diastolic murmur and a collapsing pulse appeared in the convalescent stage, and assumed that there was a direct involvement of the aorta by the spirochætal infection, in analogy to syphilitic aortitis: this interpretation, however, is hardly acceptable and it is very unlikely that there was any correlation between the aortic regurgitation and the spirochætal infection. Dawson and Hume (1916-17) were the first to report an instance of a cardiac disorder that arose in the course of spirochætal jaundice and appeared to bear a definite relation to it. This occurred in the form of paroxysmal auricular fibrillation which persisted for five days; it was confirmed by polygraphic tracings. Costa and Troisier (1917) observed four cases in which transient dilatation of the heart appeared without any other cardiac manifestations. Marchal, Soulié, and Roy (1935) reported one with transient cardiographic changes consisting of a slight prolongation of the P-R interval and abnormal T waves, and also with a presystolic gallop rhythm and a low blood pressure: no electrocardiograms were reproduced in the original paper and the patient was having digitalis, which makes the interpretation of these findings rather difficult. Clapper and Myers (1943) published two cases with cardiac complications: in one, there was a delayed auriculo-ventricular conduction which lasted seven days; in the other a pericardial friction rub and auricular fibrillation appeared during the height of the illness, persisting respectively for one and two days.

Pathological material in fatal cases in man and in experimental spirochaetosis. Mollaret and Ferroir (1935) reported a case in which the autopsy revealed parenchymatous and interstitial changes in the heart, the nuclei showing swelling and chromatolysis and the interstitial tissue being infiltrated by lymphocytes and polymorphonuclear leucocytes. Beitzke (1916) observed perivascular cellular infiltration in the myocardium. Ashe, Pratt-Thomas, and Kumpe (1941) described a case in which, in the authors' own words, "the myocardium certainly showed severe toxic damage, and although this is common in severe toxæmia, the vacuolization and loss of striation and hyalinization of portions of muscle bundles are suggestive of injury of a type that is rather characteristic of the muscular damage that occurs in Weil's disease." Raun-Byberg (1941) published a case of spirochaetosis complicated by fatal myocarditis, but the original paper was not available to us and we are unable to give any details on the nature of the myocardial involvement in this case. Löffler (1934) reported two cases of acute leptospiral vegetative endocarditis in which he was able to demonstrate spirochætes in the vegetation.

Hæmorrhages in the endocardium, myocardium, and pericardium in fatal cases in man and in experimental spirochætosis in guinea-pigs have been observed by several authors. Dawson, Hume, and Bedson (1917) found in inoculated guinea-pigs widespread hæmorrhages in several organs, including the heart, and they were able to demonstrate spirochætes in the heart muscle. Martin and Pettit (1919) observed minute myocardial hæmorrhages in inoculated guinea-pigs and also mentioned the presence of spirochætes in the heart muscle. The presence of spirochætes in the heart muscle in man was stressed by Kaneko (1917). Stokes and Ryle (1916) mention in their paper a fatal case, in the care of Capt. Floor, R.A.M.C., in which the post-mortem examination revealed multiple hæmorrhages in the pericardium. Stokes, Ryle, and Tytler (1917) found hæmorrhages in the heart in two out of four fatal cases; and in inoculated guinea-pigs they found spirochætes in the heart muscle. Watson, McLeod, and Stewart (1935) observed punctiform hæmorrhages in the pericardium in a fatal case; the heart muscle was soft and flabby. Swan and McKeon (1935) found sub-endocardial and subpericardial hæmorrhages in three out of four fatal cases. Jeghers, Houghton, Rae, and Foley (1935) described hæmorrhages in the pericardium and endocardium in one case. Davidson and Smith (1936) found hæmorrhages in the pericardium in one case and in the endocardium in another; in one of these the myocardium showed fine fatty stippling of the axial portions of the fibres. In a fatal case of Clapper and Myers (1943) the epicardial surface and the endocardial surface over the chordæ tendineæ showed minute hæmorrhages.

CASE REPORT

A seaman, aged 52 years, was admitted to the Newcastle General Hospital on June 24, 1943. His illness started ten days before admission with violent sickness and pain in the legs and the back. Very soon after he became jaundiced. He had fallen into the Thames ten days prior to the onset of symptoms. Except for a syphilitic primary sore in 1918 and malaria in 1926, there was nothing of significance in his previous history.

On admission, the patient looked ill and was deeply jaundiced. The temperature was normal. The lungs were normal, the liver and spleen were not enlarged. The central nervous system appeared to be normal. On physical examination, the heart was found to be perfectly normal, the pulse of good volume and regular, 90 a minute. The urine contained bile and albumin, and the urinary deposit showed some red cells, epithelial cells, and numerous hyaline and occasional granular casts.

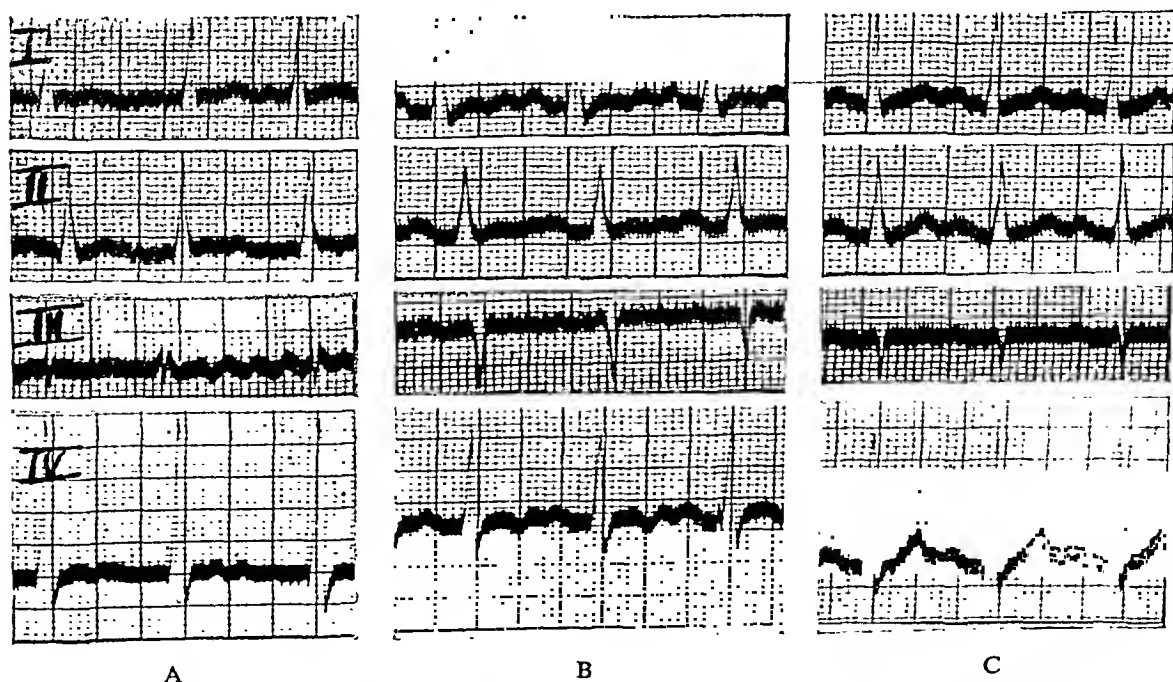


FIG. 1.—(A) Auricular fibrillation, 26/6/43. (B) Sinus rhythm with T wave changes, 30/6/43.
(C) Normal tracing, 10/7/43.

The blood urea was 175 mg. per 100 c.c. The Wassermann reaction in the blood was negative. The number of white cells was 7400 per c.mm. The diagnosis of spirochætal jaundice was made and this was confirmed by a positive agglutination titer against *Leptospira icterohæmorrhagiae* (1 : 1000, 1 : 10,000, and 1 : 30,000 on three different occasions). On June 26, the thirteenth day of the illness, the heart rhythm was found to be irregular and a cardiogram taken the same day showed auricular fibrillation (see Fig. 1A). The blood-pressure was 110/75 and the heart did not seem to be enlarged. The auricular fibrillation persisted for four days and on June 30 there was sinus rhythm with T wave changes and a P-R interval at the upper limit of normal (Fig. 1B). The blood pressure was 105/70 and there was marked asthenia. The heart sounds were distant. The size of the heart appeared to be within normal limits. A third cardiogram, taken on July 10, the twenty-seventh day of the illness, was practically normal (Fig. 1C). At that time the jaundice and the albuminuria were subsiding, but the blood pressure remained low and the temperature was now elevated. The lowest blood pressure reading, 90/70, was recorded on July 14, at a time when the renal signs cleared up completely and the blood urea became normal. Blood pressure, pulse rate, and temperature are charted in Fig. 2. After this the patient's general condition gradually improved, the temperature

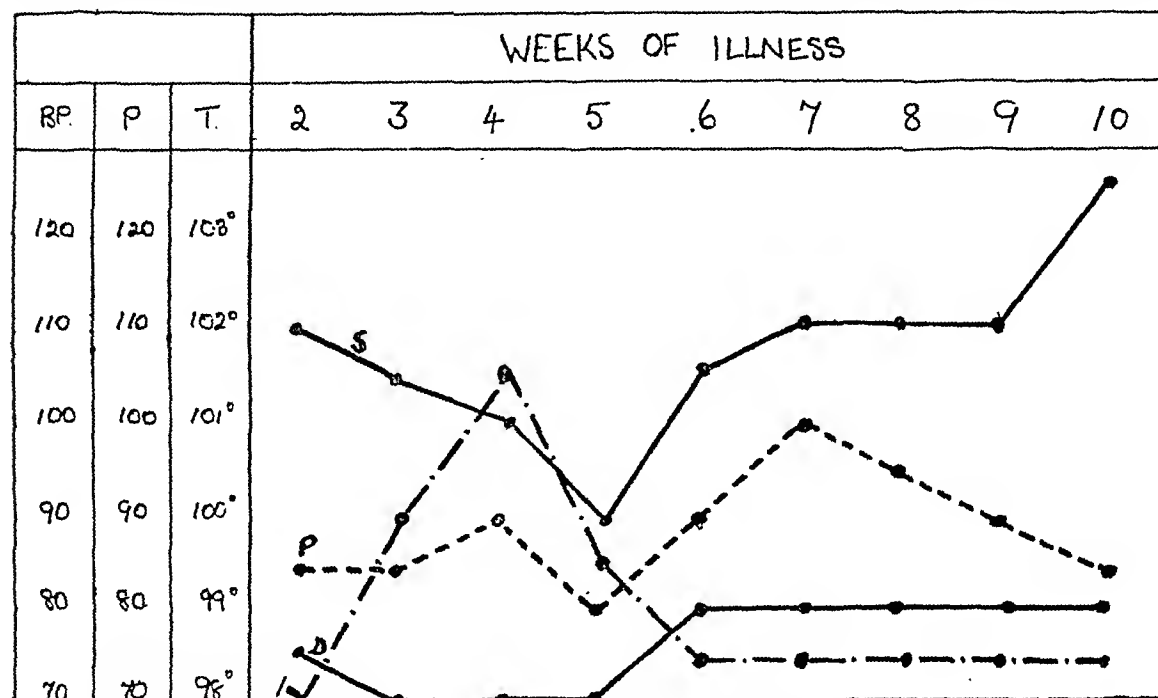


FIG. 2.—S—Systolic blood pressure; D—Diastolic blood pressure; P—Heart rate; T—Temperature. The figures represent the average reading for each week.

became normal, and the blood pressure started to rise, reaching 125/80 before his discharge in a satisfactory condition on August 25. The jaundice completely disappeared by the end of July. A screen examination on August 13 showed the heart to be normal in size and shape.

DISCUSSION

The case reported here showed evidence of a transient myocardial involvement. In the first instance it was the arrhythmia that drew our attention to the heart and prompted us to do electrocardiographic investigations. It is generally agreed that in the absence of disturbances of the rhythm the diagnosis of acute myocarditis is extremely difficult on purely clinical grounds, and as an example Saphir in his remarkable paper on myocarditis quotes Scherf and Boyd stating that "the frequency of myocarditis and the difficulty of its diagnosis are generally appreciated only after electrocardiographic studies of clinical material have been conducted regularly." If more extensive electrocardiographic studies were made in cases of spirochætal jaundice, especially in cases with very low blood pressure and changes in the character of the heart sounds, more instances of myocardial involvement might perhaps be encountered.

In the light of the anatomical findings in fatal cases in man and in experimental spirochætosis in guinea-pigs, the electrocardiographic changes can be accounted for by direct

involvement of the heart, either in the form of multiple hæmorrhages or of direct toxic damage to the heart muscle, or both. Although it is more likely that the electrocardiographic changes in our case and in the cases quoted were due to direct toxic damage to the heart muscle, hæmorrhages in the heart may have been a causative factor. We believe that widespread minute hæmorrhages in the heart, whatever the primary disease is, can produce electrocardiographic changes, especially displacement of the S-T segment and T wave changes. In support of this we mention an unreported case of traumatic asphyxia in a child, aged 5, with bluish discoloration of the chest and neck, widespread petechiæ over the upper part of the chest extending up to the neck, and subconjunctival hæmorrhages, in which we were able to demonstrate marked and transient depression of the S-T segment. We think that in this case the cardiographic changes were caused by subendocardial hæmorrhages. The pericarditis in one of the cases of Clapper and Myers (1943) appeared at a time when the blood urea was 420 mg. per 100 c.c., and it was very probably uræmic in origin. On the other hand, it is unlikely that the high blood urea, so common in spirochætal jaundice, could have been responsible for the electrocardiographic changes observed in the cases reviewed in this paper.

SUMMARY

The papers dealing with the cardiac complications of spirochætal jaundice are briefly reviewed.

One case with cardiographic evidence of transient myocardial involvement is added to those already reported.

The probable causes for the electrocardiographic changes are discussed.

We wish to thank Dr. J. A. Charles, Medical Officer of Health, Newcastle-on-Tyne, and Dr. G. P. Harlan, Medical Superintendent of the Newcastle General Hospital, for facilities provided.

REFERENCES

- Ashe, W. F., Pratt-Thomas, H. R., and Kumpe, C. W. (1941). *Medicine*, 20, 145.
 Beitzke, H. (1916). Quoted by Ashe *et al.*
 Clapper, M., and Myers, G. B. (1943). *Arch. intern. Med.*, 72, 18.
 Costa, S., and Troisier, J. (1917). *Bull. mém. Soc. méd. Hôp.*, 41, 638.
 Davidson, L. S. P., and Smith, J. (1936). *Quart. J. Med.*, 5, 263.
 Dawson, B., and Hume, W. E. (1916-17). *ibid.*, 10, 90.
 —, —, and Bedson, S. P. (1917). *Brit. med. J.*, 2, 345.
 Dräger, E. (1934). Quoted by Ashe *et al.*
 Garnier, M., and Reilly, J. (1916). *Bull. mém. Soc. méd. Hôp.*, 40, 1916.
 Jeghers, H. J., Houghton, J. D., Rae, J. H., and Foley, J. A. (1935). *Arch. Path.*, 20, 477.
 Kaneko, R. Quoted by Costa and Troisier.
 Marchal, G., Soulié, P., and Roy, A. (1935). *Bull. mém. Soc. méd. Hôp.*, 51, 1651.
 Martin, L., and Pettit, A. (1919). Quoted by Marchal *et al.*
 Mollaret, P., and Ferroir, J. (1935). *Bull. mém. Soc. méd. Hôp.*, 51, 1622.
 Raun-Byberg, J. (1941). *Ugesk. F. læger*, 103, 329.
 Saphir, O. (1941). *Arch. Path.*, 32, 1000.
 — (1942). *Ibid.*, 33, 88.
 Stokes, A., and Ryle, J. A. (1916). *Brit. med. J.*, 2, 413.
 — Ryle, J. A., and Tytler, W. H. (1917). *Lancet*, 1, 142.
 Swan, W. G. A., and McKeon, J. A. (1935). *Brit. med. J.*, 2, 570.
 Watson, G. W., McLeod, J. W., and Stewart, M. J. (1935). *Ibid.*, 1, 639.

INCOMPLETE BUNDLE BRANCH BLOCK

BY

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Lewis (1925) stated that delay in the passage of the impulse down a bundle branch could alter materially the form of the electrocardiogram. Wilson (1940) defined *incomplete* bundle branch block as due to a conduction defect that merely retards the passage of the impulse through one of the main bundle branches, and stated that it gives rise to electrocardiograms which are "transitional, both as regards the length of the QRS interval and the form of the ventricular deflections between those that represent complete bundle branch block and those of normal outline."

Partial bundle branch block is used to describe curves that contain both bundle branch block and normal complexes. There may be a rhythmic sequence, as in 2 : 1 bundle branch block, or occasional normal QRS deflections may occur in a record predominantly composed of bundle branch block complexes.

In common with the New York Heart Association's nomenclature, Wilson (1944) regards 0.12 sec. as the minimum QRS duration ordinarily compatible with the diagnosis of *complete* bundle branch block. In this country, however, a QRS that exceeds 0.10 sec. has generally been considered as indicating complete bundle branch block providing other criteria are present (Lewis, 1925; and Hunter, Papp, and Parkinson, 1940). This small divergence may be due to a different technique in measurement. In the cases to be described the QRS has been measured straight across at the widest point in any lead. In no case has it measured more than 0.10 sec., when incomplete bundle branch block has been judged to be present.

Case I. A man, aged 58, was admitted to hospital in April 1940 with a history of paroxysms of tachycardia lasting up to 24 hours during the last six months. The B.P. was 220/120. The heart was enlarged to the left. A diastolic murmur of aortic incompetence was audible. The W.R. was negative. He had no paroxysms while in hospital.

After discharge he was seen at intervals as an out-patient, when he said he was well and free from attacks. It was later learnt from his wife that he had had many paroxysms but did not wish to re-enter the hospital.

On December 27, 1940, he reported recent nocturnal dyspnoea and oedema of ankles. The pulse was 110 with premature contractions. The B.P. was 230/150. The heart was enlarged to left and right. There was a small effusion at the base of the left lung. The liver was enlarged and tender. The blood urea was 98 mg. per 100 c.c. He was admitted and was given 0.5 mg. digoxin intravenously with 0.5 mg. orally, followed by 0.25 mg. six-hourly. On December 30 the pulse was 160. Following carotid sinus pressure it fell abruptly to 80. At the same time the ward sister reported that she was doubtful how much digitalis he was retaining since he spat out the tablets whenever he could. On the following morning he was worse. The pulse was again 160: the oedema had increased; he was orthopnoeic. It was decided to give a further dose of 0.5 mg. digoxin intravenously under electrocardiographic control. Twenty minutes after the injection he was clearly suffering from digitalis poisoning with constant retching and diarrhoea. He was given atropine and morphine but he died the same night.

At *autopsy* (Dr. S. Wray) the heart was greatly enlarged due to hypertrophy of the left ventricle. There was gross atheroma involving particularly the anterior descending branch of the left coronary, which was almost occluded. The mitral and aortic valves showed atheromatous changes on the cusps with some fibrotic contraction of the left posterior aortic cusp. There was gross atheroma of the aorta. The kidneys were granular.

A section of the myocardium supplied by the anterior descending branch shows hypertrophy of the muscle bundles with loss of staining power and cellular outline. The findings suggest that the

hypertrophied muscle has been receiving an inadequate supply of blood due to the arterial atheromatous changes.

Electrocardiograms taken prior to his final admission show that the T waves in leads I and II varied from being upright to a coved inversion. (Fig. 1). This may have been due to variations in

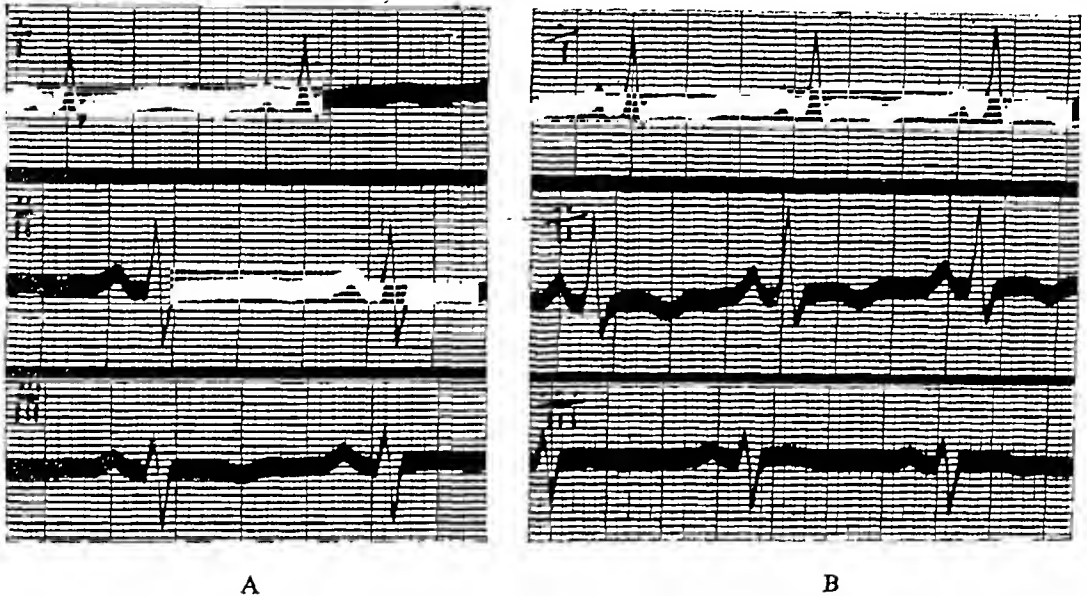


FIG. 1.—Case 1. (A) 22/7/40. T I and T II upright. (B) 11/11/40. Bowed inversion of T I and T II.

the blood supply down the anterior descending branch or possibly may be related to the paroxysms of tachycardia. Fig. 2 taken on the day of his last admission shows a ventricular rate of 116. The rhythm is normal except for auricular premature systoles, some having aberrant ventricular responses. These aberrant responses are not confined to the auricular premature systoles but follow normal P waves at the end of lead I. The fourth complex in lead I, also following a normal P wave, has a



FIG. 2.—Case 1. 27/12/40. Auricular premature contractions with aberrant ventricular responses. Aberration present also after normal P waves at the end of lead I. The fourth complex in lead I, following a normal P wave, has a deep S wave.

deep S wave. Fig. 3 shows a nodal tachycardia with a rate of 140. Fibrillary waves can be seen, especially in lead III. On account of difficulties with the light the film was thin and another was taken immediately after (Fig. 4). This shows the same nodal tachycardia with fibrillary waves but the duration of the QRS of the alternate complexes in lead I has increased to 0.09 sec. Fig. 5 was taken 15 minutes after the intravenous injection of 0.5 mg. digoxin. The ventricular rate is now 194. Alternation of the complexes is present in leads I and III, giving the appearance of a bi-directional ventricular tachycardia, but the QRS is nowhere more than 0.09 sec. The alternate complexes in lead I are similar to the isolated complex seen in Fig. 2.

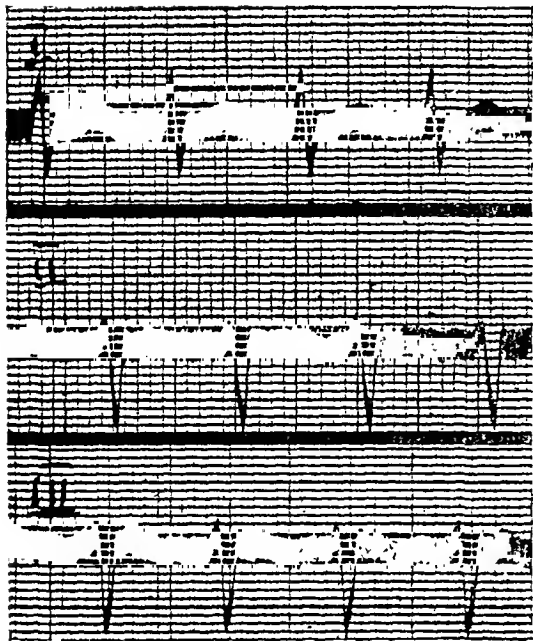


FIG. 3.—Case 1. 30/12/40. Nodal tachycardia at a rate of 140. Fibrillatory waves deforming the S-T period are visible in leads II and III.

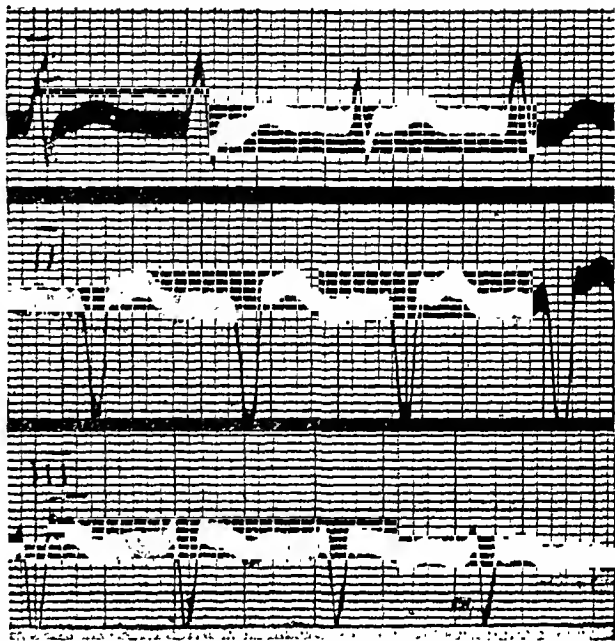


FIG. 4.—Case 1. 30/12/40. Nodal tachycardia at a rate of 132, fibrillatory waves being seen in lead II. The alternate complexes in lead I have the QRS widened to 0.09 sec.

Comment. Aberrant ventricular responses appeared first following both auricular premature beats and normal auricular beats. One of these had a deep S wave, and was interpreted as intermittent incomplete right branch block. During the early stages of the nodal tachycardia the duration of the QRS of alternate complexes increased to 0.09 sec. without any significant alteration in their shape. Finally the direction of the alternate complexes changed to that of the isolated complex of incomplete right branch block. This gave the appearance of a bi-directional ventricular tachycardia with a QRS duration of only 0.09 sec., but was due to a partial (2 : 1) incomplete right branch block.

Case II. A man, aged 60, was seen first in 1938 on account of dyspnoea on exertion. The pulse was 84; B.P., 144/84. He weighed 14 st. 6 lb. The heart was enlarged to left and right, and he had mitral incompetence. Signs of moisture were present at the bases of the lungs. He was advised to reduce his weight and his activities.

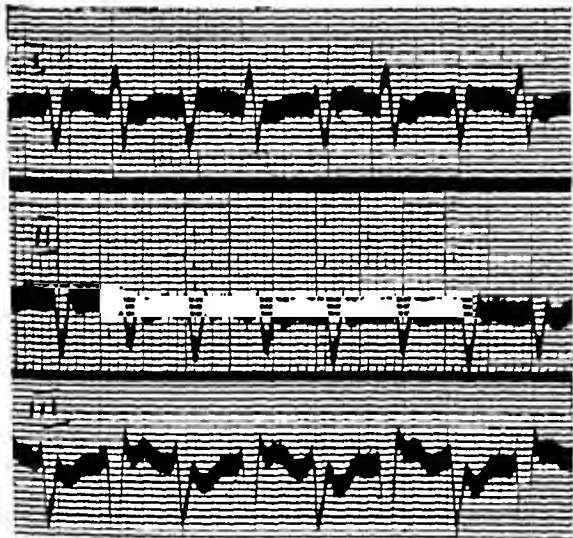


FIG. 5.—Case 1.—31/12/40. Nodal tachycardia at a rate of 194, with bidirectional ventricular responses (QRS, 0.09 sec.). Alternate complexes in lead I are similar to the isolated complex of Fig. 2. Partial (2 : 1) incomplete right branch block.

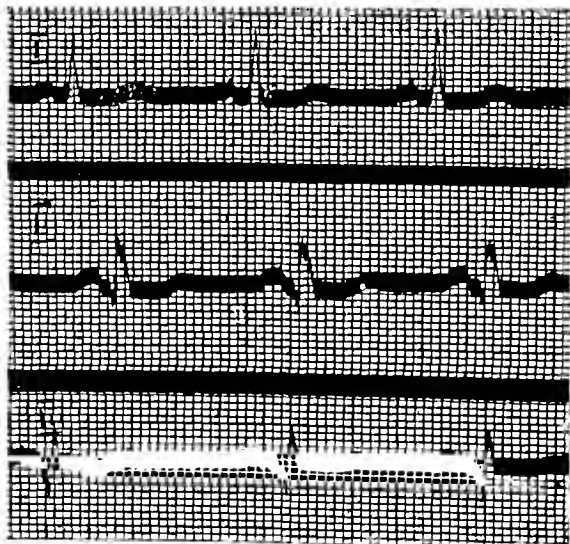


FIG. 6.—Case 2. 28/5/38. Small Q and notching of R in lead II (QRS, 0.09 sec.). Lead III, QRS "W" shaped.

In 1940 the size of the heart had increased further and digitalis was commenced in the form of Guy's pill.

In 1942 the auricles began to fibrillate and from that time he required frequent courses of neptal with ammonium chloride to avert congestive failure.

In June 1943 he suffered a cerebral embolism with temporary aphasia and an extensor plantar response on the right side. In the autumn of that year he died suddenly.

The first electrocardiogram taken in 1938 had a Q and a notched R in lead II, the QRS being 0.09 sec. In lead III the QRS is also 0.09 sec. and the deflections are "W" shaped (Fig. 6). The comment was made at the time that bundle branch block might soon supervene. This proved incorrect and the curve remained unchanged, except for the addition of many ventricular premature contractions arising singly and in couples. In 1942, after the onset of fibrillation, the ventricular complexes were virtually unaltered, but in lead III the first, third, and last complexes are quite normal (Fig. 7). Complexes of this type were never seen at any other time. In 1943 a slight widening of the QRS in lead I was observed, although the duration in that lead was still only 0.08 sec. Otherwise there was no change, but "V" leads taken at the same time show a QRS of 0.12 sec. in V.2 with a

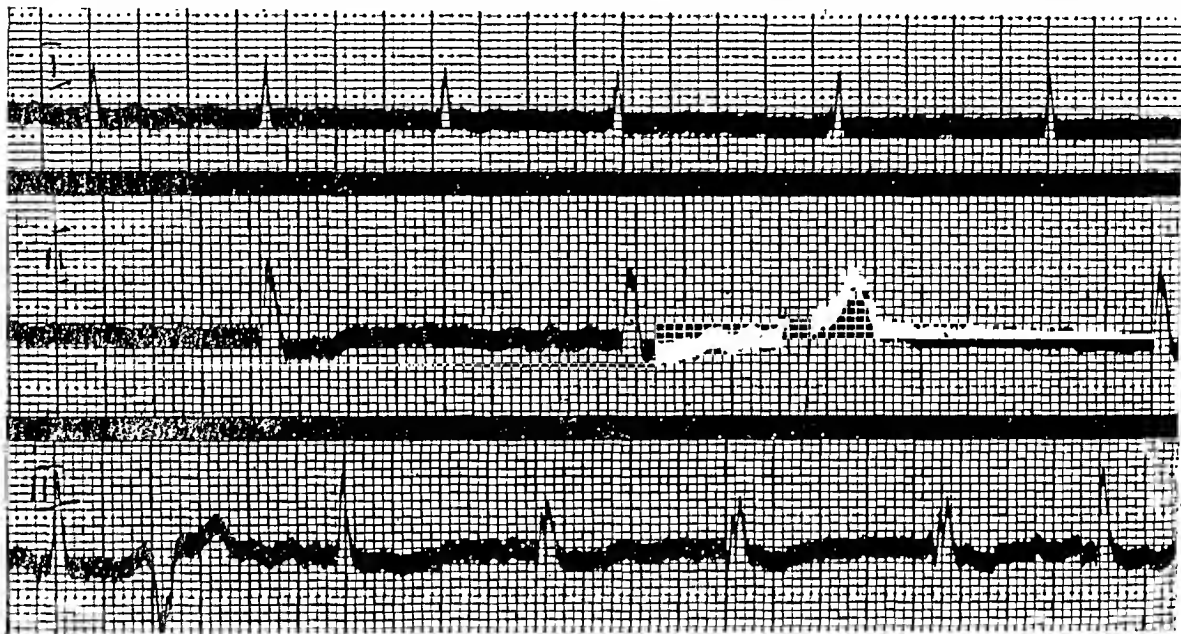


FIG. 7.—Case 2. 1/3/42. Auricular fibrillation. Basic complexes unchanged. First, third, and last complexes in lead III normal.

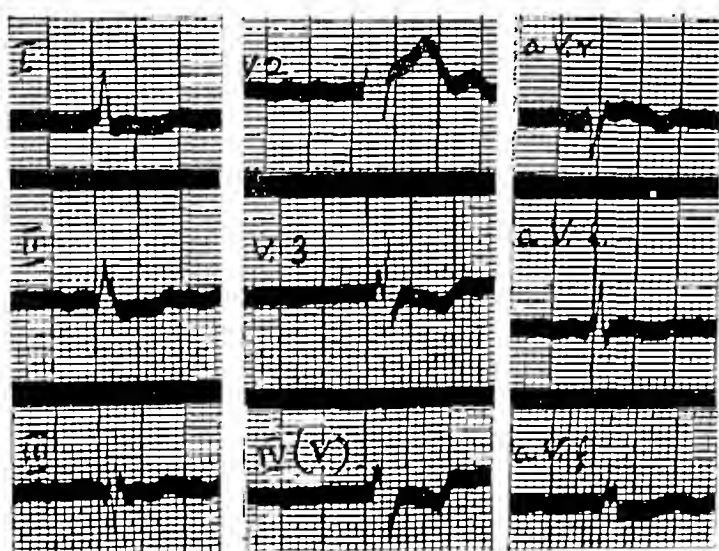


FIG. 8.—Case 2. 22/5/43. Leads I, II, and III virtually unchanged. V leads: left bundle branch block. (QRS, 0.12 sec.) Unipolar limb leads show heart in normal position.

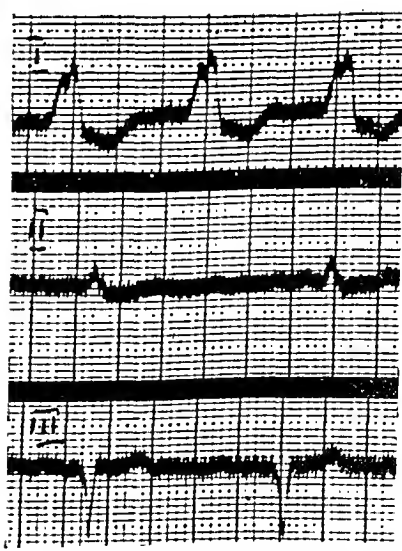


FIG. 9.—Case 2. 13/6/43. Paroxysmal left bundle branch block in lead I (QRS, 0.14 sec.).

shape characteristic of left branch block (Fig. 8). Two months later—after the cerebral embolus—a paroxysm of left branch block was recorded with a QRS of 0.14 sec. (Fig. 9).

Comment. The normal complexes seen in 1942 (Fig. 7) indicate that his usual curves were due to delayed conduction down a bundle branch. In the following year the "V" leads had the shape of a left branch block with a QRS of 0.12 sec. (the equivalent of 0.11 sec. in limb leads), and a paroxysm of left branch block was recorded two months later.

Case III. A woman, aged 81, was admitted to hospital in November 1941 on account of abdominal pain which had lasted a week. She had been breathless for some months and more recently had been orthopnoëic. The pulse was 120 and irregular from auricular fibrillation. The B.P. was 100/80. The heart was enlarged to the left: there were no murmurs. The liver was enlarged and tender. The bases of the lungs were congested. The blood urea was 113 mg. per 100 c.c. The white cells numbered 28,000.

She was given 1 grain of digitalis folia, four times daily, and three days later the rhythm returned to normal. Subsequently she developed a cerebral embolism with a left-sided facial palsy, from which she did not recover.

The cardiogram taken on 7/11/41 shows auricular fibrillation with a ventricular rate of 175. The ventricular complexes have the shape of a left bundle branch block but the QRS is only 0.10 sec.

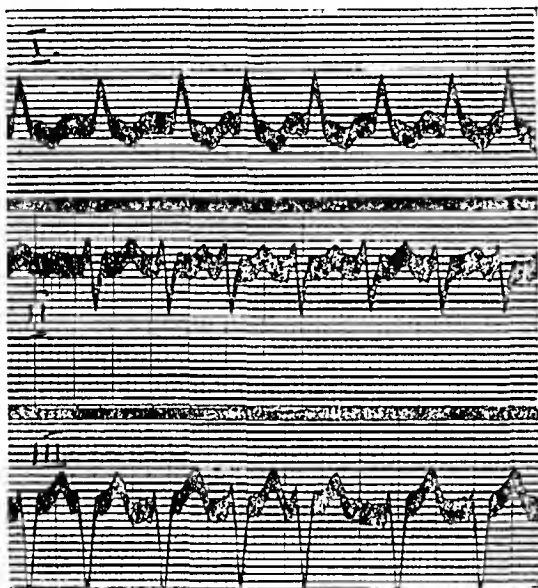


FIG. 10.—Case 3. 7/11/41. Auricular fibrillation with ventricular rate of 175. Incomplete left branch block. (QRS, 0.10 sec.)

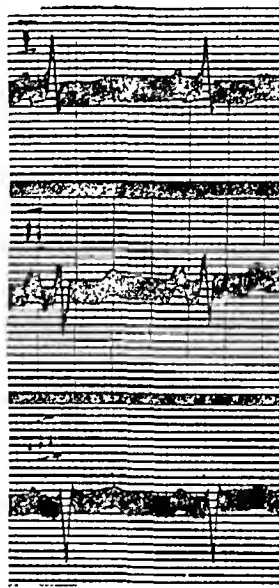


FIG. 11.—Case 3. 10/11/41. Left axis deviation. Diphasic T in lead I.

(Fig. 10). Three days later only left axis deviation is present, the QRS duration having returned to normal with the resumption of normal rhythm (Fig. 11).

Comment. The first cardiogram conforms in all respects to a left bundle branch block except that the QRS is insufficiently widened. It was interpreted at the time as indicating advanced left axis deviation or possibly incomplete left bundle branch block. The first alternative was negated by the second record.

Case IV. A man, aged 69, was admitted to hospital in 1938 on account of dyspnoea, cardiac asthma, and oedema. The B.P. was 200/110. The auricles were fibrillating. The heart was greatly enlarged to left and right. The blood urea was normal. The W.R. was negative.

He was given digitalis and injections of salyrgan with ammonium chloride, but the congestive failure was only partially relieved and he died three months later.

Several cardiograms were taken showing auricular fibrillation and inversion of T in leads I and II. In one record (Fig. 12) intermittent bundle branch block complexes occurred in leads I and II: their shape is of Type A right branch block with a QRS of 0.10 sec. A fortnight later intermittent branch block complexes were again seen in leads I and II: these had the shape of the wide SI pattern and the QRS was 0.12 sec. (Fig. 13).

Comment. The intermittent right branch block is unstable since the shape of the complexes changes. The QRS duration of 0.10 sec. in those of the first record is insufficient for complete bundle branch block.

Case V. A man, aged 74, was admitted to the surgical side of the hospital on 8/7/42 with retention of urine. He had spent the greater part of the last two years in bed on account of shortness of breath

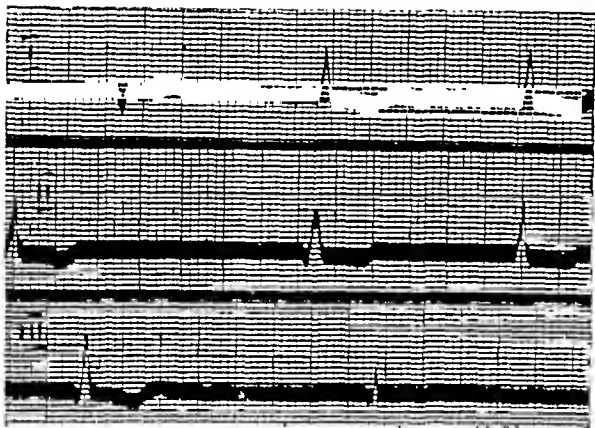


FIG. 12.—Case 4. 10/8/38. Auricular fibrillation with diphasic T waves in leads I and II. First complex in leads I and III and second in lead II have the shape of a "Type A" right bundle branch block with QRS of 0.10 sec.

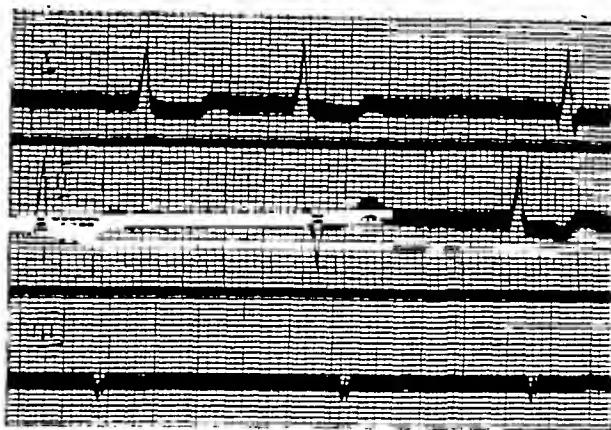


FIG. 13.—Case 4. 24/8/38. Third complex in lead I and second in lead II wide SI pattern of right bundle branch block. (QRS, 0.12 sec.)

and œdema of the legs. He had been given digitalis, but the dosage is not known. The pulse was 100 and irregular from auricular fibrillation. The B.P. was 130/90. The heart was greatly enlarged to right and left. There was œdema of the legs. The blood urea was 57 mg. per 100 c.c. The leucocytes numbered 18,000. A supra-pubic intubation (Mr. Pearce) was performed on 27/7/42. On August 1, since the rate had increased, 1 grain of digitalis folia, t.d.s. was started. This was reduced a fortnight later to 1 grain daily, and he was discharged free from œdema in September.

The first cardiogram taken on 21/7/42 (Fig. 14) shows auricular fibrillation with a partial left bundle

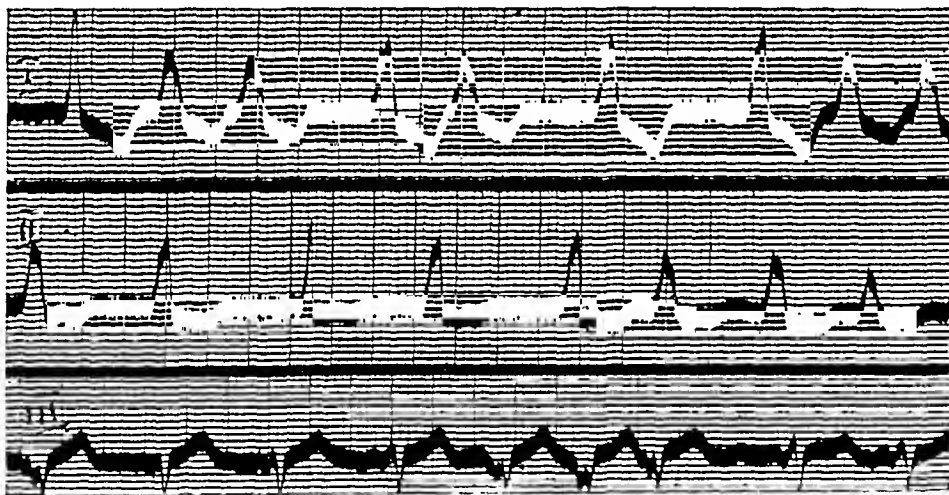


FIG. 14.—Case 5. 21/7/42. Auricular fibrillation with ventricular rate of 100. Partial left bundle branch block. (QRS, 0.12 sec.) Complexes with normal QRS duration being present in all leads. B.B.BI. complexes vary in shape.

branch block (QRS, 0.12 sec.). There is considerable variation in the shape of the ventricular complexes, and the first complex in lead I and the third in lead II together with some in lead III have QRS deflections of normal duration. In Fig. 15 (18/8/42) the QRS deflections have all a normal duration with the exception of the first two in lead I in which the duration is 0.10 sec. Auricular fibrillation persists with left axis deviation. By 10/9/42 normal rhythm has returned and the ventricular complexes have assumed a form intermediate between the two preceding curves with a QRS duration of 0.12 sec. (Fig. 16).

Comment. The QRS deflections in the first cardiogram varied considerably in shape apart from the normal complexes. When the rate was slowed with digitalis the duration of the QRS became normal but transitional complexes (QRS, 0.10 sec.) occurred. Finally bundle branch block returned, having a form intermediate between the general shape of the first record and the left axis deviation of the second.

Case VI. A woman, aged 74, was admitted to hospital on 11/1/44 under the care of Dr. Glen Reah, who kindly afforded facilities for observation. The auricles were fibrillating. The B.P. was

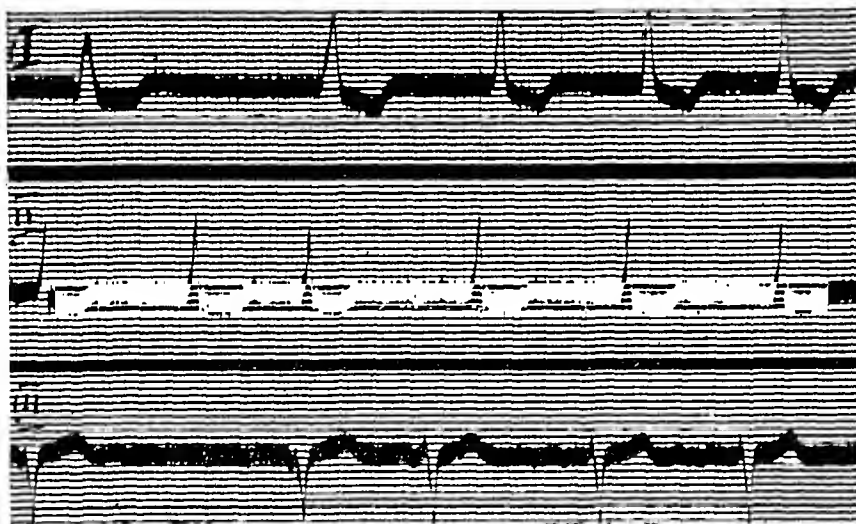


FIG. 15.—Case 5. 18/8/42. Auricular fibrillation. Left axis deviation with inversion of T in lead I and depression of S-T in lead II. The QRS of the first two complexes in lead I is 0.10 sec.

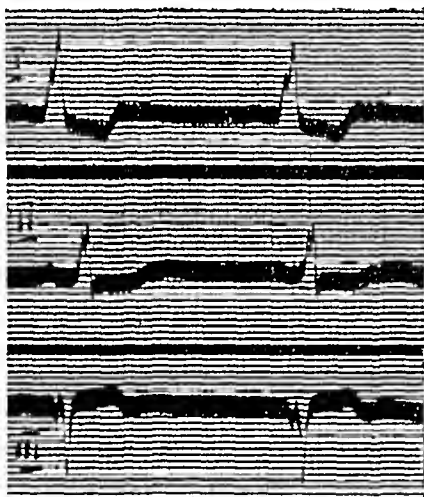


FIG. 16.—Case 5. 10/9/42. Normal rhythm. Left bundle branch block. (QRS, 0.12 sec.) Shape of complexes differs from those in Fig. 14.

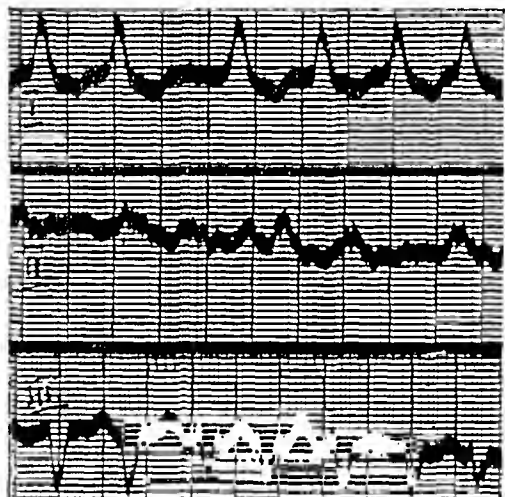


FIG. 17.—Case 6. 13/1/44. Auricular fibrillation with ventricular rate of 160. Left bundle branch block (QRS, 0.11 sec.)

100/60. The heart was enlarged to the left, and there was mitral incompetence. Crepitations were present at the bases of both lungs, and the liver was enlarged and tender. Since she had received no digitalis for the previous fortnight, it was decided to obtain a rapid effect by means of digitalis lanata. Accordingly 8 c.c. of cedilanid was given intravenously and slowing occurred within thirty minutes. Four days later normal rhythm returned, and two days later she suffered an embolism into her right leg. From this she made a satisfactory recovery without embolectomy.

The first electrocardiogram (Fig. 17) shows auricular fibrillation with a ventricular rate of 140. Left bundle branch block is present with a QRS duration of 0.11 sec. Fig. 18 taken 35 minutes after

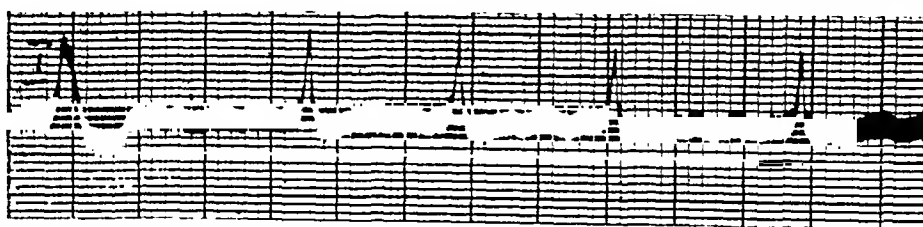


FIG. 18.—Case 6. 13/1/44. Lead I, 35 minutes after cedilanid, 8 c.c. intravenously. QRS now normal except first complex.

cedilanid shows a ventricular rate of 104, and the QRS deflections have returned to normal, except the first in the lead. Fig. 19 (17/1/44) shows the return of normal rhythm. All the ventricular complexes, with the exception of the last two in lead III (which resemble the normal complexes shown in Fig. 20),

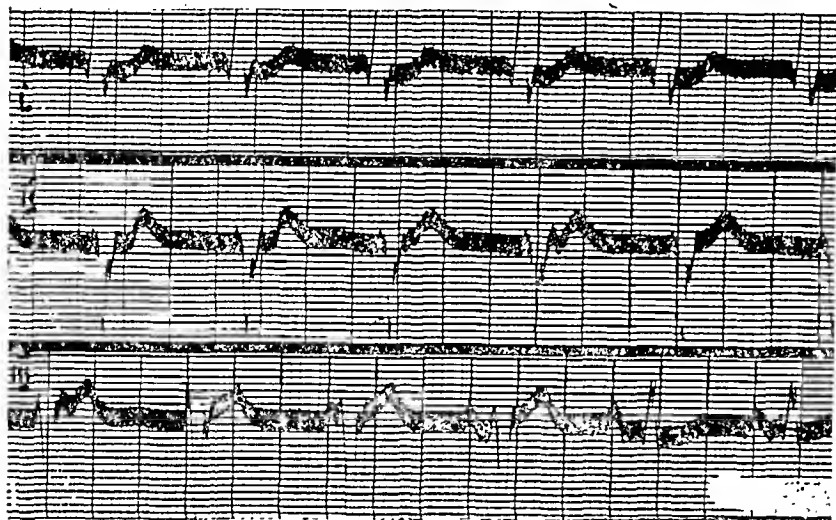


FIG. 19.—Case 6. 17/1/44. Lead I. Nodal rhythm at rate of 100: no evidence of auricular activity: incomplete right (wide SI pattern) B.B.BI. (QRS, 0.10 sec.) Lead II. Nodal rhythm at 96: P waves deforming the S-T interval of alternate complexes. Incomplete right B.B.BI. Lead III. P waves move forward from S-T till S-A node takes control at fifth complex when QRS returns to normal.

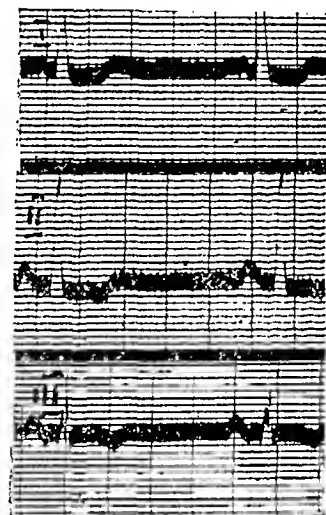


FIG. 20.—Case 6. 20/1/44. Normal rhythm. Normal QRS. Digitalis depression of S-T.

are of the wide SI type of right branch block but the QRS does not exceed 0.10 sec. In lead I there is no evidence of auricular activity, the rhythm arising from a centre in the A-V node with a rate of 100. In lead II inverted P waves can be seen deforming the S-T interval of alternate complexes. In lead III the rate has fallen to 90 and P waves can be made out in each complex. The first deforms the S-T interval, the second is almost buried in the QRS: then P moves forward until the auricle gains control of the rhythm in the fifth complex. At that point the ventricular complexes change and become normal. Later the curve reverted to partial left branch block (QRS, 0.12 sec.), normal complexes being present in leads II and III (Fig. 21). Then the duration of the QRS increased to 0.14 sec.,

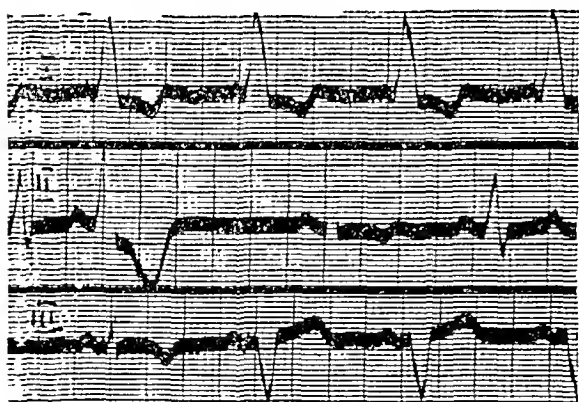


FIG. 21.—Case 6. 22/2/44. Partial left bundle branch block. (QRS, 0.12 sec.) Normal QRS follows premature systole in lead II. Normal complex also seen in lead III.

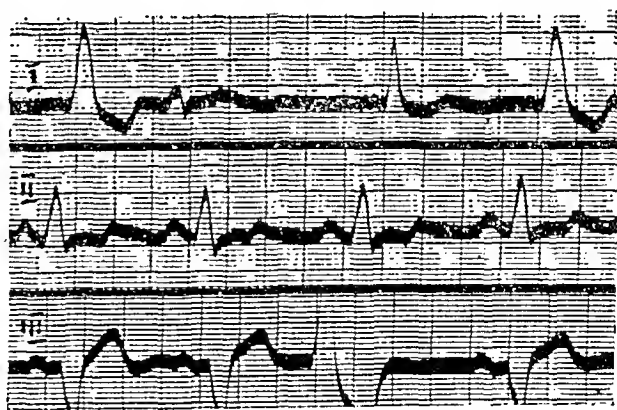


FIG. 22.—Case 6. 24/2/44. Left bundle branch block (QRS, 0.14 sec.). Transitional complex (QRS, 0.10 sec.) follows compensatory pause in lead I.

and Fig. 22 shows a transitional complex with a QRS of 0.10 sec. after the compensatory pause of a premature ventricular systole. Later again the ventricular complexes became normal.

Comment. This case shows unusual instability of the bundle branch block. The following changes were noted. Left branch block (QRS, 0.11 sec.): normal deflections after intravenous digitalis; incomplete right branch block (QRS, 0.10 sec.) shortly before the resumption of normal rhythm: normal QRS deflections; partial left branch block (QRS, 0.12 sec.): left branch block (QRS, 0.14 sec.) with a transitional complex (QRS, 0.10 sec.); normal QRS deflections.

DISCUSSION

In *complete* bundle branch block the speed of conduction down one branch of the bundle is so much slower than down the other that the impulse passes across the septum to activate the ventricle on the affected side. In *incomplete* bundle branch block the difference between the two sides is less. The affected ventricle may receive the impulse partly from across the septum and partly via its own branch, or else, when the difference is slight, wholly via its own branch though with some delay. Alternatively there may be delay in conduction down both branches caused by "a general depression of the conductivity of the Purkinje tissue" (Wilson *et al.*, 1944) and the delay may be approximately equal on both sides. Such cases might be expected to show a slight increase in the duration of the QRS with minimal changes in the shape of the complexes, and nothing to show a predominant lesion in either branch. These changes are sometimes seen in the aberrant ventricular responses that often follow premature auricular systoles, or are found in auricular tachycardia or flutter (Slater, 1930).

There are thus three groups: those with bilateral bundle branch delay, shown by a widened QRS without axis deviation (Case 1); those with delay in either right or left branch (Cases 1, 2, 3, 4, and 6); those showing a combination of the two (Cases 5 and 6).

In Case 1 slightly widened QRS deflections occurred first after auricular premature systoles, and later at every alternate beat. There was little alteration in the shape of these complexes and they are likely to be due to delay in conduction down both branches.

The last curve of Case 1 showed a bidirectional type of tachycardia with alternate complexes pointing downwards, and the same shape was seen earlier in an isolated complex following a normal P wave. Bidirectional tachycardia has been recorded in digitalis poisoning by Schewnson (1922) and by Luten (1925). Luten suggested that the rhythm originated from a point near the bifurcation of the main stem, and that there was impairment of conductivity down each branch alternately. However, the sequence of events in Case 1 all point to delay down the right branch only.

In Cases 3 and 4 and in the episode of right branch block in Case 6 there is no doubt as to the side affected. The curves conform in every particular to left and right branch block respectively except that the duration of the QRS is 0.10 sec. Had not normal complexes been present, either in the same record or a few days later, they might have been interpreted as showing advanced axis deviation and ascribed to hypertrophy of the muscle. This type of incomplete branch block may, therefore, be more common than is supposed. In Case 2 the standard leads, although abnormal, did not indicate any axis deviation, but the chest leads showed delay down the left branch.

Transitional complexes provide the most reliable evidence of incomplete bundle branch block, since, in the absence of complete A-V block with independent ventricular centres, they cannot be due to anything else. They are rare, being found in only two of the thirteen cases of paroxysmal bundle branch block studied by Comeau, Hamilton, and White (1938). But the branch block in Cases 5 and 6 was unstable, both showing partial branch block at times. Case 6 had no fewer than five changes in the duration of the QRS, which ranged from 0.08 to 0.14 sec. A similar example was recorded by Herrmann and Ashman (1930). In Case 5 the branch block complexes varied in shape in the first cardiogram, and differed again after the resumption of normal rhythm.

The duration of the QRS deflections in these transitional complexes was 0.10 sec. and, especially in Case 6, they did not show much axis deviation. The transitional complex in Case 6, too, occurred during a phase of left branch block (QRS, 0.14 sec.) and followed an episode of incomplete right branch block (QRS, 0.10 sec.). They are, therefore, probably due to the combined effect of a bilateral delay, accounting for some of the widening of the QRS, with additional delay down one branch leading to a moderate axis deviation, the proportion of each varying in different cases.

SUMMARY

Six cases of incomplete bundle branch block have been described. In none did the duration of the QRS exceed 0.10 sec. when incomplete bundle branch block was judged to be present. In all of the cases normal complexes have been present for comparison, either in the same record or within a short period.

The evidence suggests that the cases could be divided into three groups.

The first shows a slight increase in the QRS without axis deviation as exemplified by the aberrant ventricular response to an auricular premature systole. These are probably due to a bilateral delay down each main branch (Case 1).

The second shows delay down one branch, fulfilling the criteria for bundle branch block except that the QRS does not exceed 0.10 sec. (Cases 1, 2, 3, 4, and 6).

The third shows transitional complexes (Cases 5 and 6). In these cases it is likely that the transitional complexes were due to a combination of bilateral delay down each main branch with additional delay down one branch, since both cases had an unstable branch block which sometimes changed from right to left, and there was not much axis deviation although the QRS duration was 0.10 sec.

REFERENCES

- Comeau, W. J., Hamilton, J. G. M., and White, P. D. (1938). *Amer. Heart J.*, **15**, 276.
Herrmann, G., and Ashman, R. (1930). *ibid.*, **6**, 375.
Hunter, A., Papp, C., and Parkinson, J. (1940). *Brit. Heart J.*, **2**, 107.
Lewis, T. (1925). *Mechanism and Graphic Registration of Heart Beat*, pp. 45, 133.
Luten, D. (1925). *Arch. intern. Med.*, **35**, 87.
Nomenclature and Criteria for Diagnosis of Diseases of the Heart. New York Heart Association (1939), p. 132.
Schewenson, S. (1922). *Heart*, **9**, 199.
Slater, S. R. (1930). *Amer. Heart J.*, **5**, 617.
Wilson, F. N. (1940). *Diagnosis and Treatment of Cardiovascular Disease*. Vol. 1, p. 565, Stroud.
Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., de Oliveira, R. M., Scarsi, R., and Barker, P. S. (1944). *Amer. Heart J.*, **27**, 19.

THE PLACE OF FOLIANDRIN WITHIN THE GROUP OF CARDIAC GLUCOSIDES

BY

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The need for a home-grown cardiac glucoside has made itself felt in increasing measure during the last few years, and as a consequence a great number of plants of this country have been studied and tested for their possible content of cardiac principles. Popular medicine and the oldest botanical, i.e. biblical, literature helped to discover the way that promised the quickest success and eventually led to the pharmaceutical utilization of the leaves of the oleander bush (*Nerium oleander*).

The wild Palestinean oleander bush belongs to the species of *Apocynaceae*, containing in its leaves a glucoside which could be isolated in a pure crystalline form. The crystals are arranged in colourless tufts, the melting-point being 245° . The glucoside is optically active, rotating polarized light to the left.

Amorphous as well as crystalline substances had already been extracted from oleander leaves. Schmiedeberg (1883) was probably the first to isolate various principles from those leaves. He distinguished between neriin, nereantin, and oleandrin. Pharmacologically, he found that neriin and oleandrin exhibited a digitalis-like activity so that he called the former oleander-digitalein. French authors (Pieszcek, 1880; Leulier, 1889; and Dubigadon-Durieux, 1911) also reported isolation of cardiac principles from the bark of the Algerian variety of oleander.

Windaus and Westphall (1925) undertook the chemical analysis of these amorphous and crystalline substances. But it was not before Flury and Neumann's successful isolation of a pure crystalline product from oleander, in 1935, that the path was smoothed for the study of the chemical constitution. The results of these studies can be summarized as follows: oleandrin is optically active, rotating the light to the left, and upon hydrolization yields an aglycone, the oleandrigenin, which is identical with acetyl-gitoxigenin. Moreover, a sugar-residue, the "oleandrose," is split off, in which, however, none of the sugars so far known to play a part in digitalis chemistry could be identified (Shoppee, 1942).

The physical and chemical data reported by various authors for the sorts of oleandrin hitherto isolated show much divergency; this should not, however, surprise us if we consider that the habitat of the various oleander species as well as the technical methods used also show wide variations. Certain differences have even been established between the pure oleander glucoside manufactured in this country, the foliandrin, and that described by Flury (1935). Thus, for example, foliandrin has its melting-point at 245° as compared with 249° given by Flury. One cat-unit of foliandrin is equivalent to 0.324 mg./kg., while for Flury's principle it is 0.25 mg./kg.

Clinical application also revealed differences between these two sorts of pure oleander glucosides. Thus a complete and lasting digitalis effect is attributed to Flury's principle, while the specific cardiac effect of foliandrin appears with surprising rapidity with no need

for cumulation, particularly with reference to the auriculo-ventricular conduction. It acts, in addition, as a powerful stimulus to diuresis. Two electrocardiograms from a man, aged 56, who suffered from heart failure, may serve as an illustration of the foliandrin effect in the human subject. Clinically, his heart had been found enlarged in all directions. At the time of examination, pulmonary infarction was, moreover, diagnosed. In the first there was auricular fibrillation at a rate of 190 a minute (Fig. 1, A). After he had been given foliandrin

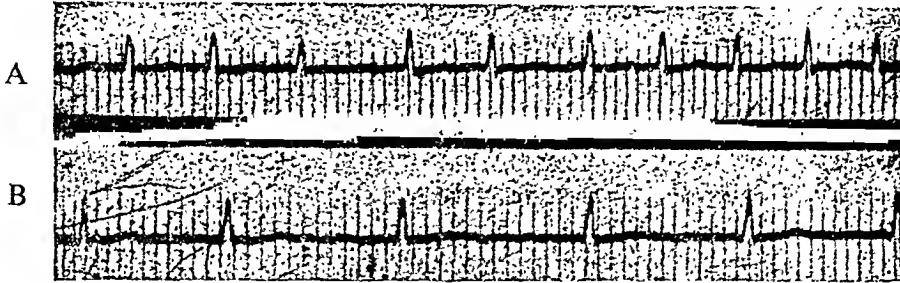


FIG. 1.—The effect of foliandrin on auricular fibrillation. (A) Before, (B) after a fairly full course by mouth.

for two days (4×50 drops per day)—which, in fact, is very near to the tolerance dose—followed by 4×1 foliandrin suppositories, the pulse rate dropped to 120 a minute on the third and to 90 a minute on the following day (Fig. 1, B).

Analysis of the clinical effect meets with a certain amount of difficulty. The time when the drug is given, the particular pathological stage, extra-medicinal factors influencing the treatment, etc., often play so vital a part that the effect of a certain principle must necessarily be different in every individual case. As clinical studies alone did not suffice, other methods had to be looked for to make it possible to assign the place to foliandrin within the group of cardiac glucosides. We tried, therefore, to get the necessary information from the reactions seen in the cardiogram of a cat after injection of one cat-unit of foliandrin. There is some diversity of opinion as to what should be deduced from the cardiographic changes occurring after administration of cardiac glucosides. The number of authors who consider the changes appearing after digitalis administration (lengthening of the P-R interval, inversion of the T wave, etc.) a specific effect of the drug is probably just as large as the number of those who attach less importance to them (Weese, 1936; Cattell and Gold, 1941; Moe and Visscher, 1938; Walther, 1904; and Brams, 1929). With due allowance for divergencies arising from the different methods, the following may be accepted. Allowing for certain variations due to dosage, anæsthetic method, and the duration of the action of the drug, the shape of the cardiogram may well be considered as characteristic, as regards the decrease in height or inversion of the T wave, the bowl-type or angulated-type of depression of the R-S-T segment, etc. These changes do not, however, suffice nor do they show a sufficiently high degree of reliability to allow of definite conclusions as to the therapeutic or toxic dosage (Gold *et al.*, 1931) of the glucoside or as to morphological changes of the heart muscle (Dearing *et al.*, 1943). However, there are two characteristic features that are, indeed, able to give information on the quality of the cardiac glucoside in question, viz. the onset of sinus bradycardia and of ectopic beats, especially if the doses employed are those established as fatal for the particular experimental animal.

This is corroborated by two papers published quite recently. In the article published by Dearing, Barnes, and Essex (1943) the great number of variations of the electrocardiogram appearing upon administration of the various cardiac glucosides are set in relation to morphological changes of the heart muscle. Krueger and Unna (1942) followed up these changes over the whole period during which the glucoside effect took place, grouping them according to the nature of the glucoside as well as to the doses administered. They used for this purpose a recently devised "heart-rate recorder" which made it possible to trace the frequency and

regularity of the heart beat on an ordinary lamp-black kymograph. They found two main differences between the effect of digitoxin (Merck) and ouabain (Merck): ouabain reduced the heart rate as early as after 15 per cent of the fatal dose, while with reference to digitoxin, reduction of the sinus rhythm occurred only after roughly 30 per cent had been injected. Similar data were established by Bauer and Reindell (1938) by Walther (1940) and by Robinson and Wilson (1918) with a different experimental method. Another difference between the effect recorded after digitoxin and ouabain was the appearance of "irregularity of heart beats." Krueger and Unna pointed out that with digitoxin, cardiac irregularity made its appearance after 76 per cent, and with ouabain after the administration of 58 per cent of the fatal dose. It should, however, be borne in mind that the anæsthetic method employed may be the cause of deviations of up to 2 per cent. The data so far published concerning the "cardiac-irregularity dose" are 70 per cent (Planelles and Werner, 1923) and 68 per cent of the fatal dose (Bauer and Reindell, 1938).

The two characteristic features referred to above—reduced heart rate and the appearance of arrhythmia—can be objectively established, and if artificial stimuli, as strangulation or cooling, are eliminated, the changes are, in fact, only attributable to the glucoside administered. Objective recording of these changes is possible by cardiographic tracings. We, therefore, chose this method to ascertain the position of foliandrin within the group of cardiac glucosides. Since for foliandrin—provided that a certain experimental method is adhered to—the fatal dose has been established as 0.324 mg./kg. \pm S.E. of 0.019 which is equivalent to one cat-unit, it was a simple procedure to arrange for intravenous injections that would contain a quantity sufficient to produce systolic syncope in the experimental animal.

METHODS AND RESULTS

Cats weighing from 1.5 to 3.5 kg. received intravenous injections into the femoral vein of one cat-unit of foliandrin respectively in urethan anæsthesia (1.8 g./kg.) and the development of the cardiac action was followed up in the electrocardiogram until death occurred. We always took the second lead (left foreleg—left hindleg). The required quantity of foliandrin was prepared from a stock solution containing 40 mg. of foliandrin per 100 c.c. in 96 per cent alcohol. Normal saline was added to make the volume up to 10 c.c. for every injection. The time during which the solution was injected was always the same, 5 minutes. After 15, 25, 50, 75, 90, and 100 per cent of the fatal dose had been injected, a cardiogram was recorded and the further development followed up oscillographically. As soon as particular rhythmic changes made their appearance, tracings were again taken. Thus it was possible to record the entirety of the events taking place in the cat's heart from the beginning of the injection until its death. An illustration of this method, so far tried in 6 cats, is shown in Fig. 2. We only accepted the onset of slowing of the heart-rate and irregularity of the beats as an indicator of the foliandrin effect. On purpose we do not enter into detail as to the changes of the T wave or of certain intervals.

The reactions taking place in the cardiac muscle and auriculo-ventricular conduction system, if syncope is produced by foliandrin, are shown in the 12 cardiograms of Fig. 2, which were taken from a continuous 15 m. long film.

The results of the above studies show that (1) reduction of the heart rate occurs as a result of intravenous injection of foliandrin which sets in after 15 per cent of the fatal dose (=one cat-unit) has been introduced, and (2) the first signs of irregularity of the heart beat appear after 50 per cent of the fatal dose (=cat-unit) has been given.

The following table gives the data for digitalis, ouabain, and foliandrin with reference to the above mentioned signs.*

* Experiments conducted by us with digitoxin "Roche" and strophanthine (Burroughs Wellcome) have, essentially, yielded the same results as those published, although the number of data at our disposal is too small to allow of definite conclusions.

| Signs | Percentage of fatal dose after which signs appeared | | |
|--|---|-----------------|--------------------------|
| | with digitalis | with foliandrin | with ouabain strophantin |
| Slowing of heart rate | 30 | 15 | 15 |
| Irregularity of the heart beats | 70 | 50 | 60 |

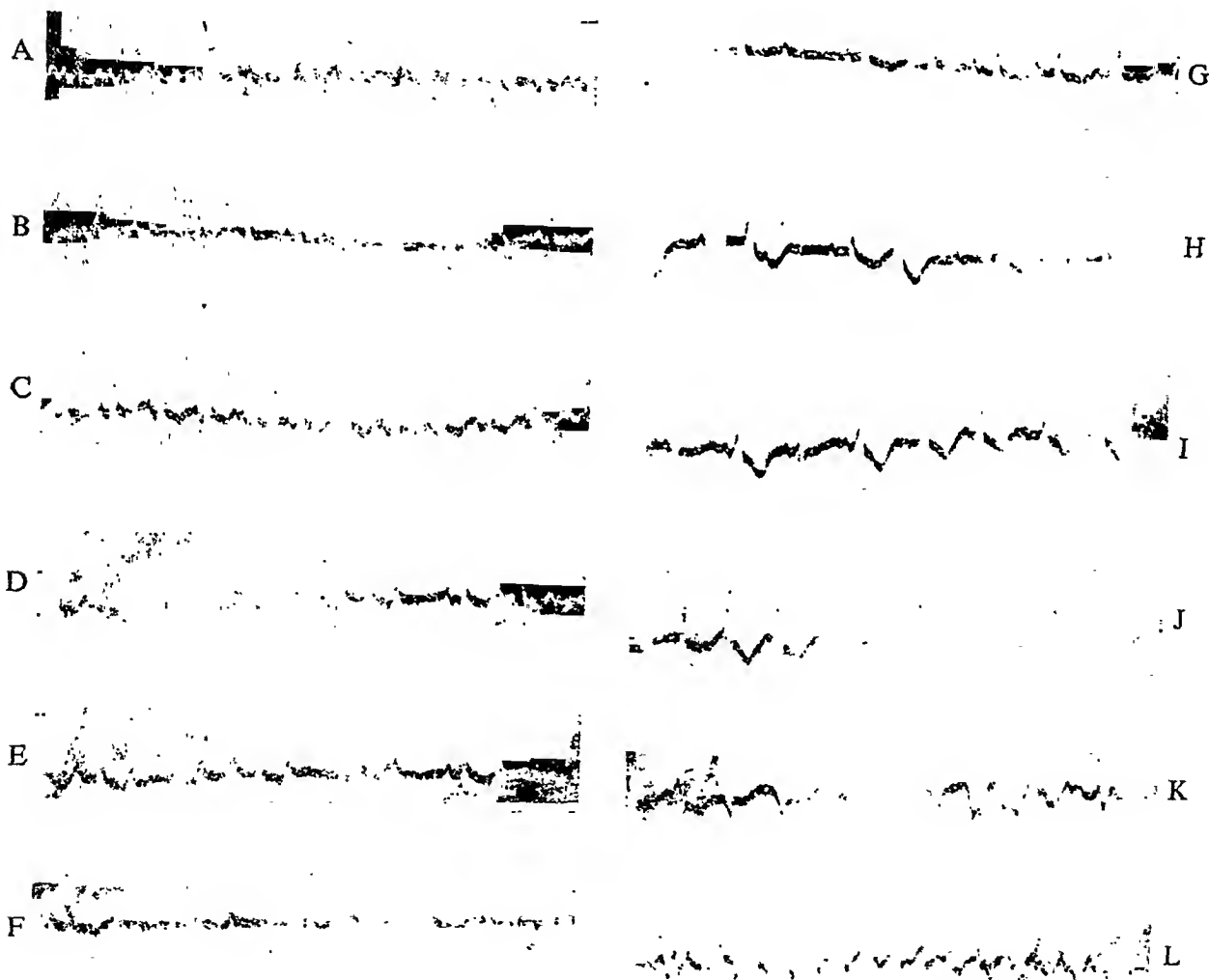


FIG. 2.—Twelve cardiograms taken on a continuous long film from a normal cat (A) Before the administration of foliandrin. (B)–(F) After the administration of various percentages of the fatal dose (=1 cat-unit). (B) After 15 per cent with some reduction of rate. (C) After 25 per cent. (D) After 50 per cent. (E) After 75 per cent, showing the first signs of irregularity. (F) After 90 per cent. (G)–(L) Terminal stages after 100 per cent fatal dose (=1 cat-unit).

Comparing the results obtained with digitalis, ouabain, and foliandrin, we may conclude that the oleander glucoside foliandrin is very closely related to ouabain, in any event belonging to the category of the strophantin glucosides rather than to that of digitalis.

These results gain particular importance in a clinical respect. Strophantin is so rapidly and completely broken down in the intestinal tract that practically no cardiac effect can be expected after oral administration, while for foliandrin clinical experience has shown that the full cardiac effect may be produced by oral administration, and that the specific effect occurs

very rapidly. It should be included in the strophantin rather than in the digitalis group, and should, therefore, be considered a "strophantinoid." As far as we know, therefore, foliandrin is the first glucoside of this group to develop its full cardiac activity in the peroral route.

The drug has so far been tested on human patients in the Hadassah University Hospital, Jerusalem, the Hadassah Municipal Hospital, Tel-Aviv, and the Government Hospital, Haifa and Jerusalem. Results will be published elsewhere.

SUMMARY

The pure glucoside foliandrin isolated from the Palestinian oleander bush (*Nerium oleander*) distinguishes itself very definitely from principles so far isolated from various oleander species. Apart from other chemical as well as physical characteristics, it could be shown by means of continuous electrocardiographic tracings from a cat's heart, that upon intravenous administration its action is identical with that of the principles belonging to the group of strophantin (ouabain) glucosides and the drug should therefore be considered a "strophantinoid." In contradistinction to strophantin, it displays its full cardiac activity upon peroral administration.

REFERENCES

- Barnes, A. R., and Essex, H. E. (1943). *Amer. Heart J.*, **71**, 114.
Bauer, H., and Reindell, H. (1938). *Arch. exp. Path. and Pharm.*, **190**, 461.
Brams, W. A., (1929). *Arch. intern. Med.*, **43**, 676.
Cattell, McK., and Gold, H. (1941). *J. Pharm. Exp. Therap.*, **71**, 114.
Dearing, W. A., and co-workers (1943). *Amer. Heart J.*, **25**, 665.
Dubigadon-Durieux, C. (1911). *J. Pharm. et Chimie*, **2**, 157.
Flury, F., and Neumann, W. (1935). *Klin. Wschr.*, **16**, 562.
Gold, H., Gelfand, B., and Hitzig, W. (1931). *J. Pharm. Exper. Therap.*, **41**, 89.
Krueger, E., and Unna, K. (1942). *Ibid.*, **76**, 282.
Laurier, J. (1889). *J. Pharm. et Chimie*, **2**, 423.
Moe, G. K., and Visscher, M. B. (1938). *J. Pharm. Exper. Therap.*, **64**, 65.
Pieszcek, A. (1880). *Arch. Pharmac.*, **252**.
Planelles, K., and Werner, H. (1923). *Arch. exp. Pathology and Pharm.*, **96**, 21.
Robinson, G. C., and Wilson, F. N. (1918). *J. Pharm. Exper. Therap.*, **10**, 491.
Schmiedeberg, O. (1883). *Arch. exp. Patho.*, **16**, 149.
Shoppee, C. W. (1942). *Aun. Rev. Biochem.*, **131**.
Walther, R. (1940). *Arch. exp. Path. Pharm.*, **195**, 709 (quoted by Krueger and Unna).
Weese, H. (1936). *Digitalis*, G. Thieme, Leipzig.
Windaus, A., and Westphall, U. (1925). *Nachr. Ges. Wissn. Goettingen, Math.-Phys.*, **78**.

TEMPORAL ARTERITIS

BY

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Temporal arteritis is a rare condition. The earliest reported cases are those of Horton, Magath, and Brown (1932) who described identical histological changes in the temporal arteries of two cases. Five years later these same authors described five additional cases. The first English papers are those of Curtis Bain (1938) and Jennings (1938). More recently the number of reported cases has been increased to some twenty by those of Bowers (1940); Sprague and MacKenzie (1940); Dick and Freeman (1940); Gilmour (1941); Hoyt, Perera, and Kauvar (1941); and Sproul (1942).

Little or nothing is known about the ætiology of temporal arteritis, and perusal of the reported cases substantiates the view that the disease is of a chronic infectious nature and is not related to either tuberculosis or syphilis. The condition occurs most often in the fifth or sixth decade and is commonest in women. Its principal symptom is headache, chiefly referred to the site of the affected vessels, and the pain is not only intractable to the usual remedies, but is also aggravated by mastication or by other movements of the jaws and face. The involved vessels feel thickened and nodular and gradually become devoid of pulsation. The disease lasts over a period of several months and most patients recover. Diagnosis rests upon a biopsy of the affected vessels, and sometimes the mere resection of a portion of the affected vessels seems to have relieved symptoms.

Horton, Magath, and Brown cultivated a strain of actinomyces from a portion of resected vessel, but did not believe that this was the cause of the disease. Sproul and Hawthorne (1937) and Gilmour (1941) showed that identical lesions may be present in the aorta and its branches, and the latter named the condition giant-cell chronic arteritis. This at least dispels the original and usual view that temporal arteritis is a localized and non-fatal malady, and indicates that temporal arteritis is but a local manifestation of a diffuse arterial disease. Among other sites where similar lesions have been described are the occipital, retinal, and radial arteries. It seems probable that the intractable headache of some cases may be due to involvement of the cerebral vessels. There does not so far appear to be any explanation for the predilection for the temporal arteries in this disease.

The histological picture of the published cases is remarkably uniform, and is that of an arteritis. The intima is greatly thickened and there may be thrombosis in the markedly reduced lumen of the vessel. The media is largely replaced by granulation tissue with fragmentation of the elastic lamina. Characteristically present in the media are giant cells with many nuclei.

REPORT OF A CASE

A. M., a labourer, aged 61, complained of rheumatic pains in the knees and shoulders for six months, and of severe headaches in the temporal and occipital regions for one month. His past history did not include any severe or important illness.

His present illness was ushered in gradually with pain in the knee and shoulder joints, and a general feeling of weakness, so that he found it difficult to get about. After a few months there was

spontaneous improvement in his joint symptoms, but he began to have very severe headaches involving the sides and back of his head. The headache was aggravated by movements of the jaw, by coughing, and by mastication. Coincidentally he noticed small tender nodules on his temples and over the occiput. The headache persisted with unabated severity and remained uninfluenced by any usual therapy. There was no disturbance of vision.



FIG. 1.—Low power view of part of a transverse section of the artery. (Stained hæmatoxylin and eosin; magnification $\times 250$.)

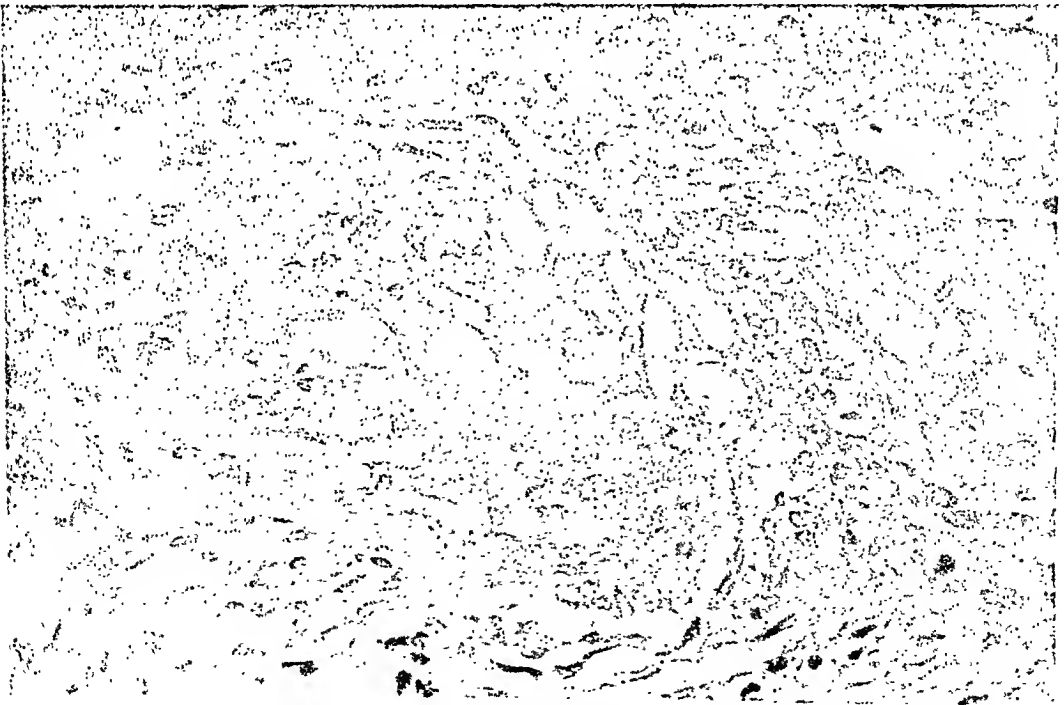


FIG. 2.—High power view of part of the same section showing a typical giant cell. (Stained hæmatoxylin and eosin; magnification $\times 550$.)

On examination he appeared to be rather thin and pale. Moderate arteriosclerosis was present. The heart was normal and the blood pressure 150/80. The lungs were emphysematous. The pupils reacted to light and to accommodation and the fundi were normal. The reflexes were all present and equal. There was some muscular wasting of the arms and legs. The joints were not swollen but coarse crepitus was present in knees and shoulders.

There was marked tenderness over the occipital and temporal areas of the scalp, particularly the latter. A number of small nodules were clearly visible and palpable over the temporal artery and similar nodules were palpable over the occiput. The temporal artery was thickened and pulsation was diminished. The nodules appeared to be in the walls of the vessel, and they were exquisitely painful on palpation; the skin overlying them was reddened. In the course of three weeks the pain subsided and the nodules disappeared. In the final stages pulsation in the affected vessels was barely apparent.

Laboratory Examinations. Blood sedimentation rate was 13 mm. in 1 hour (Westergren). Blood urea 60 mg. per 100 c.c. The red cell count was 3,670,000 per c.mm.; the hæmoglobin was 62 per cent (Haldane); the colour index 0.8, and the white cell count 7200 per c.mm. The Wassermann and Kahn reactions were negative. An electro cardiogram showed normal axis and no abnormality. An X-ray of the chest was also normal.

An initial diagnosis of periarteritis nodosa was made, but in the absence of any evidence of visceral involvement a biopsy of the temporal artery was performed, and a segment of the vessel removed. The course after operation was uneventful.

Pathological Report. The material submitted consisted of a small piece of an artery with grossly thickened wall, and a lumen that was practically occluded. The tissue was fixed in formalin, and transverse sections were prepared and stained by hæmatoxylin and eosin, Van Gieson's stain, and Verhoeff's elastic tissue stain.

Histologically, well-marked pathological changes were present, and these were found to conform very closely with the histological picture of temporal arteritis as described by Horton and Magath, and with the histological picture described in other arteries by Gilmour, and named by him giant-cell chronic arteritis.

The intima showed great hypertrophy, and the hypertrophied tissue was composed of proliferating muscle fibres supported in a mucoid ground substance. The cells in this tissue were arranged quite irregularly and the more usual arrangement into circular and longitudinal bundles was entirely absent. The elastic lamella was fragmented and in certain areas it could not be demonstrated. In a few areas in the intima giant cells could be seen, but they were very few as compared with those in the media, and much smaller in size.

The media showed chronic inflammatory changes with lymphocytic infiltration and giant-cell formation. These giant cells showed very large numbers of nuclei and appeared to be of foreign body type for the most part. In appropriately stained sections it could be seen that in some instances these giant cells were in intimate relationship to small fragments of elastic tissue.

The changes in the adventitia were relatively slight as compared with those in the other two coats, but signs of an inflammatory process were present here as well. There was some infiltration with lymphocytes and a few plasma cells could be seen, along with small numbers of epithelioid cells. The small branches of the artery outside the adventitia did not show any pathological changes. In both intima and media wide capillaries were present.

The picture is thus one of chronic granulomatous, giant-celled arteritis, affecting primarily the media of the artery, but showing changes in all three coats.

SUMMARY

A case has been described in which the clinical and pathological findings are those of an arteritis of the temporal arteries. Perusal of the reports of similar cases suggests that temporal arteritis is but a local manifestation of a general disease of the arterial tree.

Our thanks are due to Mr. Warwick Bailey for the excision of the biopsy specimen, and to Drs. W. W. Woods and J. R. Gilmour for their opinions on the histological material.

REFERENCES

- Bain, C. W. C. (1938). *Lancet*, 1, 517.
 Bowers, J. M. (1940). *Arch. intern. Med.*, 66, 384.
 Dick, G. F., and Freeman, G. (1940). *J. Amer. med. Ass.*, 114, 645.
 Gilmour, J. R. (1941). *J. Path. Bact.*, 53, 263.
 Horton, B. T., Magath, T. B., and Brown, G. E. (1932). *Proc. Staff Meet. Mayo. Clinic.*, 7, 700.
 Horton, B. T., and Magath, T. B. (1937). *Arch. intern. Med.*, 53, 400.
 Hoyt, L. H., Perera, G. A., and Kauvar, A. J. (1941). *New England J. Med.*, 225, 283.
 Jennings, C. H. (1938). *Lancet*, 1, 424.
 MacDonald, J. A., and Moser, R. H. (1936-7). *Ann. intern. Med.*, 10, 1721.
 Sprague, P. H., and MacKenzie, W. C. (1940). *Can. med. Ass. J.*, 43, 562.
 Sproull, E. E. (1942). *New York State J. Med.*, 42, 345.
 — and Hawthorne, J. J. (1937). *Amer. J. Path.*, 13, 311.

NICOTINIC ACID IN THE TREATMENT OF ANGINA PECTORIS

BY

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Glyceryl trinitrate has had no equal in the relief and prevention of the anginal attack. The claims of new drugs must, however, be tested if their pharmacological action includes dilatation of the coronary artery and if clinical benefit has been observed.

Since improvement in patients with angina pectoris has been reported recently by Moncrieff (1942) and Neuwahl (1942) from treatment with nicotinic acid, it became necessary to test the drug in a series of cases under controlled conditions. Moncrieff recorded benefit in three patients with doses varying from 10 to 50 mg. by mouth. Neuwahl claimed prolonged improvement in six patients after intravenous administration: one of these had received anti-syphilitic treatment for aortitis, another showed aortic incompetence and great dilatation of the aorta, and a third with mitral stenosis was subject to paroxysmal auricular fibrillation; electrocardiography was not a part of the examination, and no mention was made of the period of rest associated with the nicotinic acid infusions of which six were given within three weeks. Transient benefit was also claimed from oral administration of the drug, but no dosage was mentioned. Masek (1940) watched temporary improvement in four cases of old cardiac infarction, and in three with coronary sclerosis and angina pectoris, after the intravenous injection of the chloride of nicotinic acid in doses up to 0.16 g. He suggested that this effect might not only be due to coronary dilatation but also to an improvement in the metabolism of the myocardium by saturation with coenzymes.

The conversion of sugar to pyruvic acid and lactic acid occurs in a series of steps through intermediary substances so that a gradual supply of energy is liberated in the tissues (Eddy and Dalldorf, 1941). Involved in the type of oxidation which is based on hydrogen transfer, are many factors including "hydrogen acceptors," such as nicotinic acid amide. This is combined in the molecules of coenzyme I (diphospho-pyridine-nucleotide) and of coenzyme II (triphospho-pyridine-nucleotide) which are sometimes collectively termed the V factor. In man the administration of nicotinic acid causes a considerable rise in the level of the V factor in the blood (Kohn, Klein, and Dann, 1939) which should in theory assist the removal of lactic acid and other products of metabolism from the myocardium. If the accumulation of such substances plays some part in the causation of anginal pain, a rise in the coenzyme level of the blood and tissues should be beneficial in myocardial ischaemia. For this purpose the amide of nicotinic acid would be as efficacious as nicotinic acid itself, but would cause no vasodilatation (Field and Robinson, 1940).

Rachmilewitz and Braun (1944) discussing the cardiographic changes in nicotinic acid deficiency have assumed that an altered metabolic state of the heart is due to lack of coenzyme. In spite of the fact that the nicotinic acid intake on an average middle-class diet is perilously low (Kodicek, 1942), even minor degrees of deficiency must be very uncommon in this country. It is significant too, that I have found no reference to the common association of angina pectoris with pellagra, even in the elderly. In view of the possibility that an increment in coenzymes might mitigate the anginal pain, the amide of nicotinic acid has been employed as well as nicotinic acid in the present clinical trial.

The cutaneous response to nicotinic acid in the form of flushing has shown great variation not only in different subjects, but in the same subject at different times (Spies, Bean, and Stone, 1938; Sebrell and Butler, 1938). Although occasional flushing may result from doses as low as 25 mg., doses upward of 500 mg. are required to produce for certain a degree of peripheral effect. Experimental proof of general systemic vasodilatation and clinical observation in the

treatment of peripheral vascular disease have been disappointing. Popkin (1939) found that variations in surface temperatures were inconstant and that the amplitude of oscillometric readings actually diminished in most cases. Other investigators (Abramson, Katzenstein, and Senior, 1940) showed that a significant increase of blood flow was generally elicited in the hand and forearm with only a slight increase in the leg. As regards coronary dilatation there is as yet no definite evidence that this is produced by nicotinic acid. Quite apart from the inconstancy of vasodilatation as measured by peripheral flushing, the reaction does not take place for 10 to 20 minutes after the drug is taken by mouth and lasts a similar time. The peripheral effects, to say the least, are unpleasant ; and nicotinic acid on this account would be unpopular for routine use if flushing were an essential aim.

DESCRIPTION OF CLINICAL TRIAL

In this investigation cases of angina pectoris were selected according to the criteria adopted by Evans and Hoyle (1933). Thus each patient had angina pectoris of effort, characterized by sub-sternal pain that spread across the chest, often through to the back, or to the shoulders, down one or both arms, or occasionally to the jaw and neck. The attack was always determined by physical exertion. Emotion sometimes induced an attack in some of the cases, but only where physical movement would bring on the pain as readily. Eight of the ten patients had had cardiac infarction at some previous date, but sufficient time had elapsed for maximum myocardial recovery to occur ; one of the remaining two had hypertension, and the other with classical anginal attacks had a normal cardiogram. All cases were studied as ambulant out-patients. Clinical examination included cardioscopy and cardiography and a Wassermann reaction was sometimes taken. The drugs given and doses employed are indicated in Table I. Each test period lasted at least one week, and this was often repeated. There was no particular sequence, and a placebo in the form of ascorbic acid or a gentian mixture was interspersed at intervals. All drugs were taken orally and swallowed, except for glyceryl trinitrate which was chewed. Nicotinic acid was employed in doses of 50 to 100 mg. prophylactically, and for the direct relief of the painful attack in some of the cases. In all cases during further trial periods it was given in regular doses of 25 or 50 mg., up to 200 mg. daily. Similarly nicotinamide was given in amounts up to 400 mg. in a day. It will be observed from the tabulated results that no greater benefit resulted from nicotinic acid or from nicotinamide than from a placebo. Improvement or deterioration that occurred during

TABLE I

EFFECT ON PAIN IN 10 PATIENTS WITH ANGINA OF NICOTINIC ACID AND NICOTINAMIDE COMPARED WITH THAT OBTAINED FROM PLACEBO AND GLYCERYL TRINITRATE

| Drug | Dose and Method | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---------------------|---|----|----|----|----|----|----|----|----|----|----|
| Nicotinic Acid | 50-100 mg. for relief and prevention. | | — | | — | | — | | + | | |
| | Up to 200 mg. daily in 3 or 4 doses. | + | — | — | — | + | — | — | + | — | — |
| Nicotinamide | 200-400 mg. daily in 4 doses. | — | + | + | — | — | + | + | — | — | — |
| Ascorbic Acid | For relief and prevention, 3-4 doses daily. | + | — | + | — | + | — | + | — | — | + |
| Gentian Mixture | Three doses daily. | + | + | — | — | | — | — | | — | |
| Glyceryl Trinitrate | For relief and prevention. | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |

++ indicates great benefit ; +, slight benefit ; —, no benefit.

the trial periods could be explained by the natural variation in the severity and frequency of anginal attacks associated with or apart from changes in external influences. Thus, nicotinic acid failed to fulfil the postulates suggested by Evans (1944) as forming a statutory standard of efficiency for drugs. On the other hand great benefit was obtained in each patient from the use of glyceryl trinitrate; it quickly relieved the attack when it had developed, and greatly reduced the number of attacks when a tablet was chewed before any exercise that customarily induced pain.

Toxic effects. Bean and Spies gave nicotinic acid to over a thousand subjects without toxic effects (Bicknell and Prescott, 1942). A fall in blood pressure from 190/100 to 110/80 was reported by Popkin (1939) after the administration of 100 mg. of nicotinic acid to a woman of 50 with essential hypertension. Other unpleasant effects after the oral administration of large doses have been reported, including true angor animi in one subject (Spies, Bean, and Stone 1938), dizziness, nausea, cramp in the epigastrium, vomiting, mental depression, palpitation, and urticaria. In the present trial severe flushing effects were reported by four patients. One felt tightness in the chest after a dose of 50 mg. and had to discontinue the drug because of faintness after taking eleven such doses within three days. His pain became worse. Another patient felt giddy after 50 mg., but later did not particularly mind a severe flushing reaction after 100 mg. The other two tolerated flushing well, but had no relief from pain. As expected, no such peripheral reactions occurred after nicotinamide.

ELECTROCARDIOGRAPHIC CHANGES

Irregularities in the R-T segment and the T wave associated with anginal pain have been described by Parkinson and Bedford (1931) and by Goldhammer and Scherf (1932), but there

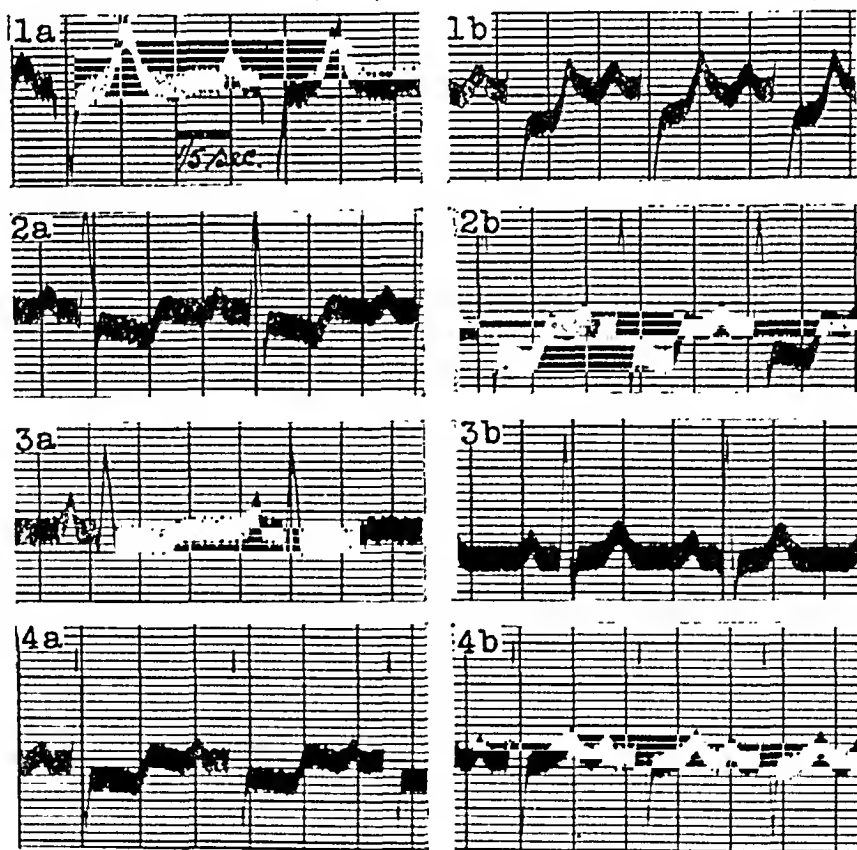


FIG. 1.—Changes in the electrocardiogram (lead IVR) of a patient with cardiac ischaemia, following the administration of nicotinic acid and glyceryl trinitrate (see next page).

- (1a) at rest. (1b) after exercise inducing pain.
- (2a) at rest. (2b) 25 minutes after 200 mg. nicotinic acid which failed to cause flushing.
- (3a) at rest. (3b) 24 minutes after 300 mg. nicotinic acid which caused generalized flushing.
- (4a) at rest. (4b) 4 minutes after chewing glyceryl trinitrate gr. 1/100.

is a difference of opinion as to the frequency and character of such cardiographic variations (Freedberg *et al.*, 1941). These changes induced by anoxæmia have been employed by Levy and others (1939) as a test for coronary efficiency. Glyceryl trinitrate may correct such cardiographic variations (Evans and Hoyle 1933); so that the effect of nicotinic acid upon the abnormal electrocardiogram was tested in one case. In this patient exercise in the form of raising and lowering the legs to a standard height from the couch caused depression of the R-T segment.

The effect of nicotinic acid in preventing and correcting this deformity was observed and compared with that produced by glyceryl trinitrate (Fig. 1). When 200 mg. of nicotinic acid was given by mouth it did not cause flushing, neither did it prevent pain induced by exercise, nor R-T depression in the cardiogram. After 300 mg., which produced a severe flush, pain and R-T depression were prevented until the flush was passing. Absence of pain and cardiographic changes were noted on one occasion when flushing was induced by 150 mg. It has been widely assumed that depression of the R-T segment and inversion of the T wave associated with exercise are indications of coronary insufficiency. If these cardiographic changes are prevented by a drug administered before exercise, or corrected should they have already taken place, it might be reasonable to deduce that coronary blood flow has been improved thereby. Further observations on the effects of known coronary dilators on such cardiographic changes need to be carried out. Meanwhile these results appear to indicate that coronary dilatation does accompany the peripheral vascular effects of nicotinic acid, but that flushing is necessary and is variable in development even with large doses. After glyceryl trinitrate with the exception of periods when records were made at 4, 6, and 8 minutes after the tablet was chewed, exercise was continued until the patient was tired and breathless. No pain nor R-T depression resulted.

CONCLUSIONS

Changes in the electrocardiogram of cardiac ischæmia in man, following the administration of nicotinic acid, suggest that the drug can improve coronary blood flow; but this only results from a dosage large enough to produce peripheral flushing, which in itself is an uncertain and unpleasant effect.

In a controlled clinical trial no improvement resulted from the oral administration of nicotinic acid in moderate dosage, either in the prevention or relief of angina, and nicotinamide in larger doses failed to give better results.

Once again glyceryl trinitrate has shown that it has no equal in the treatment of angina pectoris, and nicotinic acid has no claim to routine use in this complaint.

I am indebted to Dr. William Evans for his advice in the preparation of this paper, and to Dr. E. Miles for facilities for the investigation.

REFERENCES

- Abramson, D. I., Katzenstein, K. H., and Senior, F. A. (1940). *Amer. J. med. Sci.*, 200, 96.
 Bicknell, F., and Prescott, F. (1942). *The Vitamins in Medicine*. London.
 Eddy, W. H., and Dalldorf, G. (1941). *The Avitaminoses*. Baltimore.
 Evans, W. (1944). *Brit. med. J.*, 1, 371.
 Evans, W., and Hoyle, C. (1933). *Quart. J. Med.*, 2, 311.
 — (1933). *Lancet*, 1, 1109.
 Field, H., and Robinson, W. D. (1940). *Amer. J. med. Sci.*, 199, 255.
 Freedberg, A. S., Riseman, J., and Spiegel, E. D. (1941). *Amer. Heart J.*, 22, 494.
 Goldhammer, St., and Scherf, D. (1932). *Z. Klin. Med.*, 122, 134.
 Kodicek, E. (1942). *Lancet*, 1, 380.
 Kohn, H. I., Klein, J. R., and Dann, W. J. (1939). *Biochem. J.*, 33, 1432.
 Levy, R. L., Bruenn, H. G., and Russell, N. G. (1939). *Amer. J. med., Sci.*, 197, 241.
 Masek, J., and Svatos, F. (1940). *Casop. lek. Cesk.*, 79, 793.
 Moncrieff, A. (1942). *Lancet*, 1, 633.
 Neuwahl, F. G. (1942). *Ibid.*, 2, 419.
 Parkinson, J., and Bedford, D. E. (1931). *Ibid.*, 1, 15.
 Popkin, R. J. (1939). *Amer. Heart J.*, 18, 697.
 Rachmilewitz, M., and Braun, K. (1944). *Ibid.*, 27, 203.
 Sebrell, W. H., and Butler, R. E. (1938). *J. Amer. med. Ass.*, 111, 2286.
 Spies, T. D., Bean, W. B., and Stone, R. E. (1938). *Ibid.*, 111, 584.

PULMONARY EMBOLISM: THE CLINICAL AND CARDIOGRAPHIC PROGRESS OF A CASE

BY

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Although severe pulmonary embolism is not an uncommon complication of abdominal operations, the opportunities for a close clinical study of the condition are few. Too often the medical officer arrives at the bedside when it is too late. Even those patients who do not succumb at once rarely survive a few hours. In such circumstances, emergency measures connected with treatment take the place of clinical observations, which might include cardiographic records.

The account that follows is about a patient who developed severe pulmonary embolism, eight days after abdominal hysterectomy, and was observed continuously from the onset of the embolism until recovery took place.

CASE NOTES

A woman, aged 42, was admitted to hospital for the investigation of ascites, which had lately set in with shortness of breath and anorexia. A hard and slightly tender nodular mass, rising out of the pelvis to the left of the midline, was considered to be an ovarian cyst and probably malignant. At laparotomy, free fluid was found in the peritoneal cavity; it had arisen in connection with papilliferous ovarian cysts, one of which had ruptured. The uterus, densely adherent to the bladder and rectum, was successfully removed with both cysts, which proved to be carcinomatous on microscopic examination.

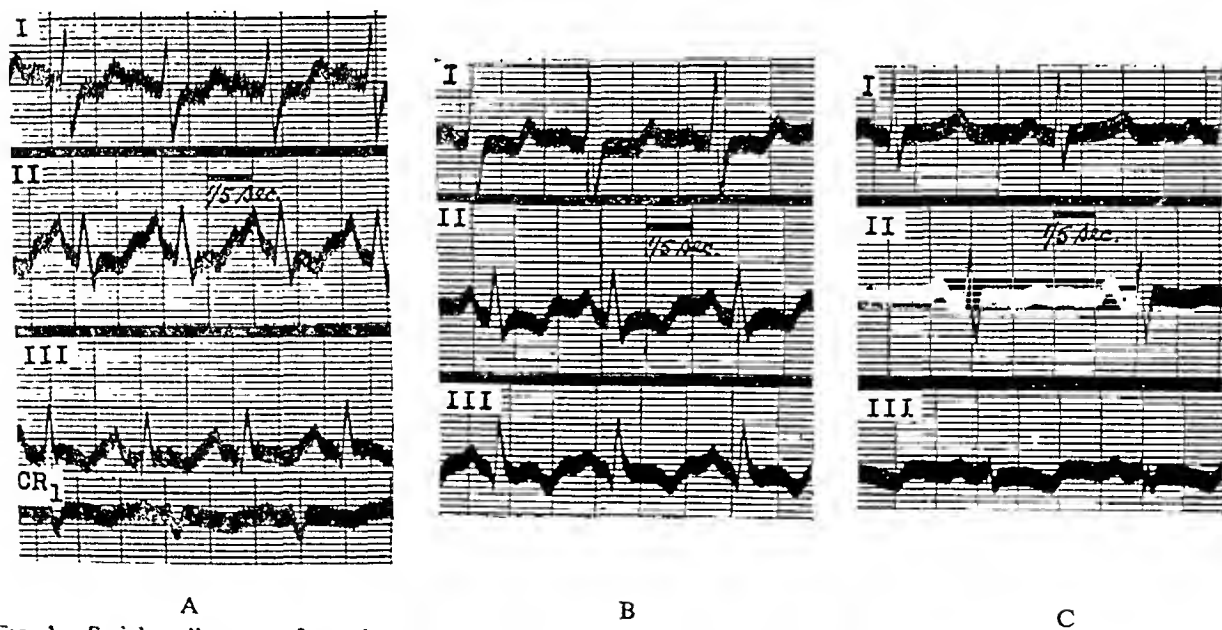


FIG. 1.—Serial cardiograms after pulmonary embolism (20/5/43), with inversion of T in leads II, III, and CR₁ (see p. 163).
(A) 20/5/43, the same evening. (B) 21/5/43, the next day. (C) 25/5/43.

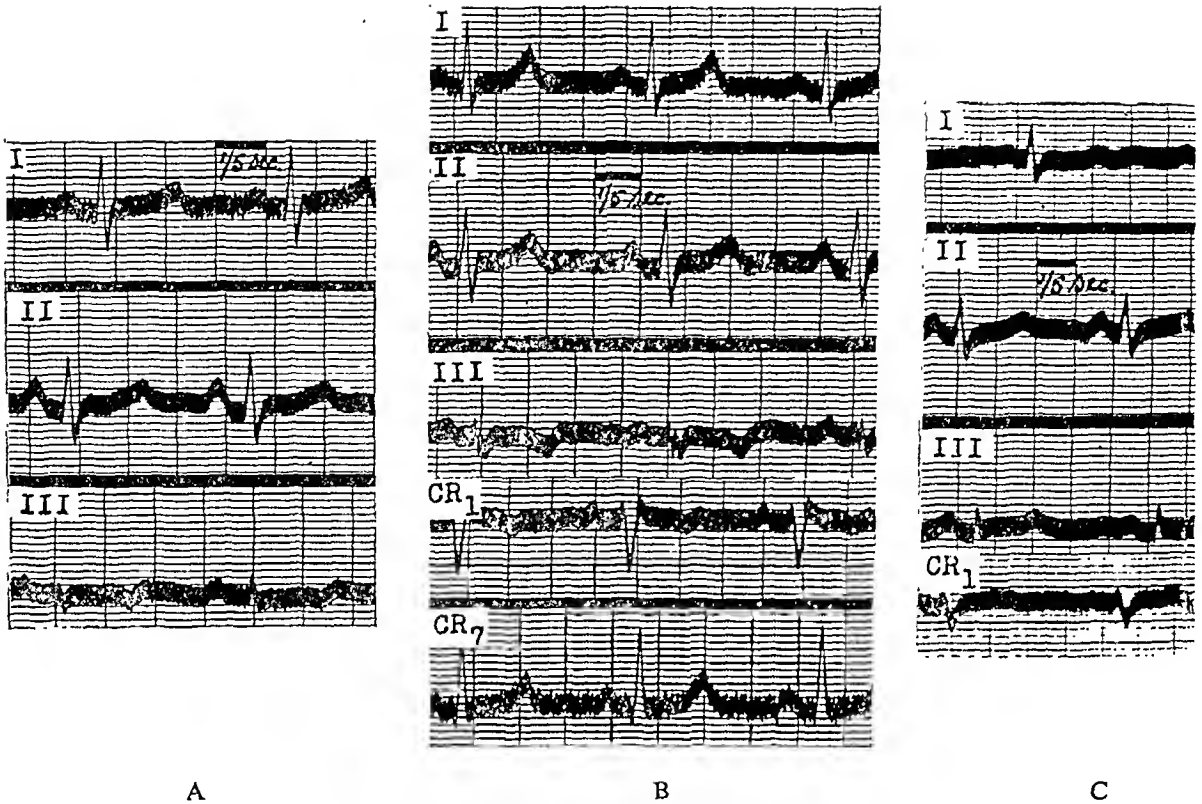


FIG. 2.—Subsequent cardiograms showing recovery.
 (A) 27/5/43, and (B) 1/6/43, with inverted T III. (C) 9/7/43, with upright T III.

On the eighth day after operation, the patient had a feeling of tightness across the chest and some breathlessness. The symptoms increased during the afternoon, and that evening the discomfort had given way to a feeling of suffocation. She called a nurse who noticed that the breathing had become distressed and that the pulse could not be felt. Five minutes later the patient became suddenly very dyspnoëic and turned ashen grey. Gasping violently for breath, she called out "Give me air or I will die." Within thirty seconds she lost consciousness and became pulseless. The pupils dilated widely and the corneal reflex disappeared. There was spontaneous evacuation of urine and fæces.

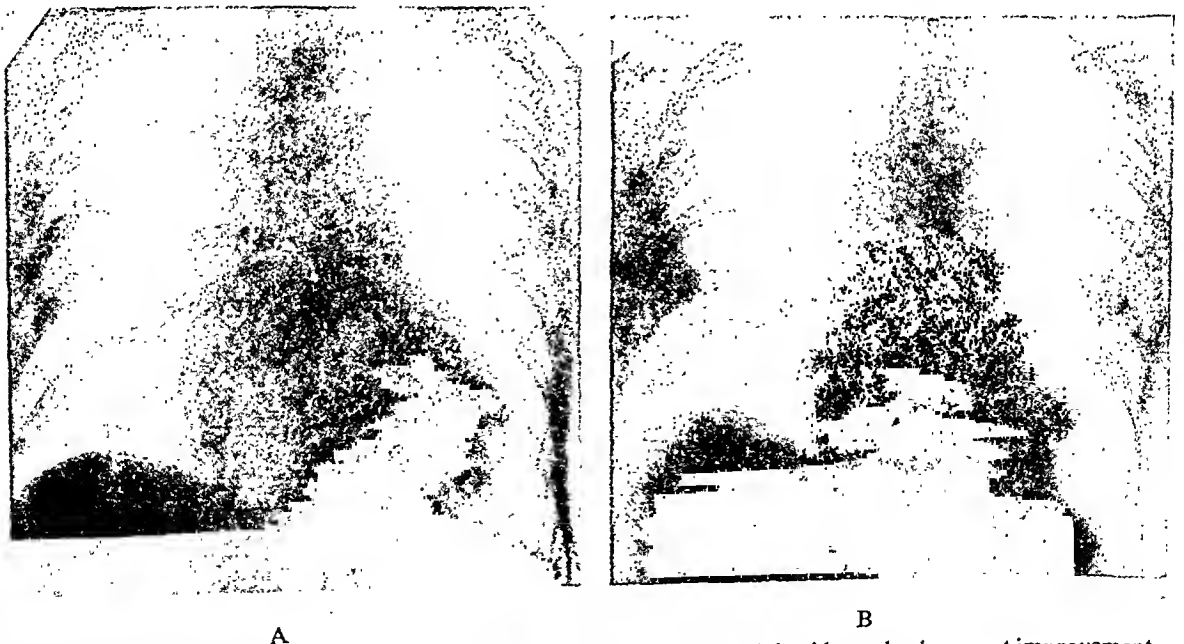


FIG. 3.—Teleradiograms showing cardiac enlargement, especially of the right side, and subsequent improvement.
 (A) 21/5/43, fourteen hours after pulmonary embolism. (B) 27/5/43.

On auscultation of the heart, an obvious triple rhythm was heard, internal to the apex. Accurate placing of the additional heart sound was impossible at the time, owing to the severe tachycardia (140 a minute). The respiration, at first deep and rapid, became shallow and more rapid (40 a minute) during the period of unconsciousness, which lasted three minutes. The patient suddenly regained full consciousness, sweated profusely, and spoke in a whisper to those at the bedside. The pulse returned. In half an hour the respiration rate had returned to 18 a minute and distress was absent, although exhaustion was still present. The pulse continued to be small and rapid (132 a minute) and the blood pressure was 90/80. The apex beat could not be felt. The heart sounds were distant and there was accentuation of the pulmonary second sound. The triple rhythm persisted.

Next day the patient's condition deteriorated rapidly; the pulse rate dropped from 120 to 76, and the respirations became slow and deep; but these changes did not last and improvement again took place. With the slower heart rate it was possible to tell that the triple rhythm was caused by the addition of the third heart sound. The blood pressure also improved to 115/75. Harsh breath sounds were heard over the midzone of the left lung but no dullness or moist sounds developed. There was great improvement in the patient's condition on the third day and her recovery appeared to be assured. On the fourth day after pulmonary embolism triple rhythm gave way to dual rhythm, and the blood pressure rose to 130/85. The patient remained apyrexial throughout the illness. There was at no time any complaint of cough or sharp pain in the chest, and hæmoptysis was absent. Oxygen was administered from the onset of the illness and was continued for 25 hours. In the hope of preventing the spread of thrombosis 20,000 units of heparin were administered intravenously on the first day, and 5,000 units two hourly for four doses when di-coumarin (100 mg. by mouth daily for 14 days) was substituted. With the object of decreasing arterial spasm at the site of the embolus, 1 c.c. of eupaverin was given intramuscularly 4-hourly for four doses. Frequent cardiograms were recorded throughout the illness. They confirmed the diagnosis of sudden failure of the right heart and served as an index of recovery of the heart. The serial tracings (Fig. 1 and 2) showed right ventricular preponderance and inversion of the T waves in leads II, III, and in CR₁; the T wave in CR₇ was upright. Serial telerradiograms (Fig. 3) were also taken and these showed alteration in the size of the heart contingent with the severity and duration of the obstruction in the pulmonary circulation. They failed to reveal any evidence of pulmonary infarction.

DISCUSSION

The observations of McGinn and White (1935) that consistent variations from the normal appeared in the cardiograms of a number of their patients developing pulmonary embolism have given impetus to the study of the behaviour of the heart in this condition. Their results have been repeatedly confirmed and extended by numerous workers, particularly by Barnes (1936), who tabulated in detail the diagnostic features of the limb lead changes occurring in pulmonary embolism, and by Wood (1941), who directed attention to the significance and importance of multiple chest leads in the differential diagnosis of acute cor pulmonale. In spite of these notable advances, as Murnaghan and others (1943) have pointed out in a review of 102 cases of pulmonary embolism, confusion is liable to arise in an interpretation of the cardiographic changes, unless a distinction is made between cases with and without acute cor pulmonale and cases with and without pre-existing heart disease. Furthermore it is only by assigning a case of pulmonary embolism to its appropriate category that a correct interpretation of the clinical and cardiographic findings is possible. The case reported, having developed a severe degree of acute cor pulmonale in the absence of pre-existing heart disease, affords a good opportunity for undisturbed observation of the effects on the heart of pulmonary embolism, and has allowed its close study which has already extended over twelve months. In addition, certain clinical observations, dating from the moment of embolism, early cardiographic tracings and serial radiograms of the heart have yielded information in regard to the mechanism of acute cor pulmonale.

Pulmonary obstruction compatible with survival. Experimental evidence would indicate that pulmonary obstruction may be considerable without extinguishing life. Thus, Haggart and Walker (1923) by quantitative closure of the pulmonary artery in cats found that, when up to 52 per cent of the lumen was occluded, few ill-effects were observed, but that when occlusion exceeded 66 per cent the animals invariably died. Clamping the left pulmonary artery raised the pulmonary arterial pressure by 29 per cent and the respiratory rate by 25 per cent without

altering the size of the heart, the cardiac output, or the systemic arterial blood pressure. From the clinical aspect, the findings of Thompson and Evans (1930) show that the upper limit of acute depletion of the pulmonary circulation compatible with survival, is under 50 per cent. Studying the problem of paradoxical embolism and its relation to pulmonary embolism, they concluded that if 50 per cent or more of the pulmonary circulation be cut off suddenly by an embolus, death results within 10 to 30 minutes. Thus in 18 cases of pulmonary embolism, in which embolus was the cause of death proved at autopsy, 16 showed depletion of the pulmonary circulation by 50 per cent or more; only one of these 16 cases had survived a period of 30 minutes.

Severe pulmonary obstruction without infarction. The clinical, radiological, and cardiographic evidence in the case reported, indicates severe initial pulmonary obstruction which became steadily regressive and finally ceased. The most likely explanation for this behaviour—applicable to other cases of acute cor pulmonale which survive—is that much of the severe but temporary obstruction is caused by vasospasm throughout the pulmonary tree as a result of the embolism (Jesser and de Takáts, 1941). This explanation is rendered all the more certain in the present case, in that there was neither clinical nor radiological evidence of pulmonary infarction. Such negative evidence would also indicate that the embolus initiating pulmonary obstruction was of small size. It is not easy to envisage an embolus that could bring about a severe degree of obstruction by virtue of size alone being driven into the pulmonary tree and yet failing to produce an infarct. But even allowing that the embolus were small, why did it not declare itself by signs of pulmonary infarction? The only explanation accounting for such a contingency is found in the unusually rich anastomosis existing between the bronchial and pulmonary arteries, preventing pulmonary infarction. Anastomoses of this kind, an exaggeration of the normal, are seen for example in a gross and chronic form in congenital pulmonary atresia.

The clinical diagnosis of acute cor pulmonale. McGinn and White (1935) described acute cor pulmonale as the result of sudden distension of the right ventricle and right auricle which might follow obstruction to the pulmonary artery by an embolus. The condition can frequently be recognized by a knowledge of the previous history and by attention to the early symptoms and signs as typified by the present case. Severe initial shock, pallor, cold extremities, great dyspnoea, and low blood pressure are important signs in the clinical diagnosis of acute cor pulmonale. Thus Murnaghan and others (1943) in two series of cases of pulmonary embolism, presenting with and without signs of shock, found cardiographic evidence of acute cor pulmonale in just over half of the first group and in under a quarter of the second. Distension of cervical veins, although not recorded in the present case, is claimed by Wood (1941) to be present in all cases of acute cor pulmonale in which this sign is sought within the first three days of embolism. After this period venous distension is often absent.

A physical sign of great diagnostic value is the early appearance of triple rhythm due to the third heart sound. Within a few minutes of embolism in the present case a distinct triple rhythm was heard, and although its exact nature during tachycardia was difficult to interpret it became obvious when the beat slowed. Triple rhythm in acute cor pulmonale has been recorded by several observers (Murnaghan *et al.*, 1943; Wood, 1941), but without emphasis on its value in clinical diagnosis. The addition of the third heart sound, when not a physiological finding in young adults, is a reliable clinical index of right-sided heart failure (Evans, 1943). Thus it was commonly heard in mitral stenosis, hypertensive heart failure, emphysema, and congenital heart disease.

The early appearance of the third heart sound in the present case was clinical proof of acute cor pulmonale because of the known absence of previous heart disease. This sign should rank high amongst the clinical criteria by which the diagnosis of acute cor pulmonale is determined. Less severe pulmonary embolism producing lesser degrees of acute cor pulmonale may not show triple rhythm, and recourse to electrocardiographic records may be necessary

to supply evidence of right ventricular stress, but it suggested that every case of pulmonary embolism presenting triple rhythm (Type Ib of Evans) demonstrates acute cor pulmonale as well, provided that pre-existing heart disease can be excluded.

Changes in the size of the heart. Cardiac enlargement, predominantly of the right side, shown radiologically 14 hours after embolism (Fig. 3), would indicate that actual distension of the right ventricle and right auricle was an important factor in determining the striking initial cardiographic changes, which persisted in a modified and steadily regressive form for a period of seven weeks. Besides demonstrating that acute ventricular distension, compatible with survival, can take place in the absence of radiographic evidence of pulmonary infarction, the X-ray appearance of the heart is in keeping with the post-mortem findings of right ventricular and right auricular enlargement evidenced in some fatal cases of pulmonary embolism.

Electrocardiographic changes. Cardiographic irregularities in pulmonary embolism are characteristic, and when present they confirm the presence of acute cor pulmonale. Briefly they are, prominent S I with the S-T segment starting slightly below the base line; depressed RS-T segment in lead II, with gradual ascent from the S to the T wave in the same lead; usually a diphasic or monophasic T II; the presence of a Q wave and definite inversion of T in lead III (McGinn and White, 1935); sharp inversion of T without appreciable displacement of the RS-T segment, always in CR₁, and sometimes for shorter duration in IV R; T in CR₁ commonly remains inverted for several weeks; less essential is a tendency for the QRS deflection to be mainly upward in CR₁ (Wood 1941).

My case showed such changes, some of them strikingly. Right axis deviation was noteworthy, with an unusually deep S I and sharp inversion of T in leads II, III, and CR₁. Thus the cardiographic records confirmed the conclusions reached in regard to the early appearance of the third heart sound and the radiographic evidence of right ventricular distension. The chest leads show that recovery was delayed longest in CR₁, and that even after seven weeks, the T wave although upright was low. Thus, T in CR₁ is the most sensitive cardiographic index we possess for determining the presence of right ventricular strain. The direction of the T wave in lead CR₇ should be noted. Evans and Hunter (1943) in describing this lead implemented it in distinguishing between T II and T III inversion of posterior cardiac infarction and similar changes seen in heart failure in emphysema and in pericardial and congenital heart disease. In these conditions T in CR₇ is positive, with recognized exceptions, while the reverse is usually the case in posterior cardiac infarction. In my case, therefore, a positive T in CR₇ demonstrates that their observations apply equally to a condition characterized by acute right ventricular failure as they do to the chronic forms of right sided failure which they described.

Myocardial ischæmia—resulting from coronary insufficiency and variously attributed to increased tension in the right ventricle, shock, asphyxia, fall in systemic arterial pressure, and reflex changes in the coronary circulation—has been put forward to account for the cardiographic changes in pulmonary embolism (Horn *et al.*, 1939). Although cardiac ischæmia undoubtedly takes place in the development of acute cor pulmonale and may even proceed to cardiac infarction, in the absence of coronary occlusion (Currens and Barnes, 1943), it cannot be advanced as the cause of the limb lead changes. Wood (1941) had demonstrated that although the limb lead changes in pulmonary embolism and posterior cardiac infarction may simulate each other, the chest lead changes in the two conditions are entirely different. More recently (Evans and Hunter, 1943) the CR₇ chest lead has helped in the differential diagnosis as instanced by my case. Further, the similarity of cardiographic behaviour in pulmonary embolism and in conditions characterized by chronic right ventricular strain, points to acute right ventricular stress as being the cause of the cardiographic changes in pulmonary embolism. Cardiographic changes similar to those seen in pulmonary embolism may be recorded in pulmonary stenosis, mitral stenosis, and chronic cor pulmonale (Selzer and Wood, 1939), while in rheumatic carditis, which may be associated with isolated right ventricular failure, Wood

(1941) has recorded transient changes, indistinguishable from those found in pulmonary embolism.

SUMMARY AND CONCLUSIONS

A case of pulmonary embolism with acute cor pulmonale is described. A severe degree of cor pulmonale developed in the absence of radiological evidence of pulmonary infarction.

Emphasis has been placed on the value of triple rhythm, from the addition of the third heart sound, in the diagnosis of suspected cases of pulmonary embolism.

Radiographic evidence of distension of the right auricle and right ventricle is related to the onset and duration of the cardiographic changes. Inversion of the T wave in CR₁ is probably the most sensitive of the cardiographic indices of right ventricular failure. The value of this change and of findings in lead CR₇ in the diagnosis of acute cor pulmonale from posterior cardiac infarction is confirmed.

I wish to thank Dr. R. Sleigh Johnson, under whose care the patient was admitted to the Southend General Hospital, for his permission to publish this case and for the interest he has shown in this work. Particularly do I wish to thank Dr. William Evans for his constant encouragement and for his helpful criticism of this paper. The keen co-operation of Miss Peach, technician to the Cardiac Department, and of Mr. W. E. Beadle, who took the radiographs, is much appreciated.

REFERENCES

- Barnes, A. F. (1936). *Proc. Staff Meet., Mayo Clin.*, **11**, 11.
Currens, J., and Barnes, A. R. (1943). *Arch. intern. Med.*, **71**, 325.
Evans, W. (1943). *Brit. Heart J.*, **5**, 205.
— and Hunter, A. (1943). *Ibid.*, **5**, 73.
Haggart, G. E., and Walker, A. M. (1923). *Arch. Surg.*, **6**, 764.
Horn, H., Dack, S., and Friedberg, C. K. (1939). *Arch. intern. Med.*, **64**, 296.
Jesser, J. H., and de Takáts, G. (1941). *Arch. Surg.*, **42**, 1034.
McGinn, S., and White, P. D. (1935). *J. Amer. med. Ass.*, **104**, 1473.
Murnaghan, D., McGinn, S., and White, P. D. (1943). *Amer. Heart J.*, **25**, 573.
Selzer, A., and Wood, P. (1939). *Brit. Heart J.*, **1**, 49.
Thompson, T., and Evans, W. (1930). *Quart. J. Med.*, **23**, 135.
Wood, P. (1941). *Brit. Heart J.*, **3**, 21.

CONGENITAL PERICARDIAL DEFECTS

BY

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Congenital pericardial defects are among the most uncommon of reported cardiac anomalies. In 1925 Moore was able to find 64 references to pericardial defects, but a detailed re-examination of the records by Southworth and Stevenson in 1938 reduced the number of confirmed cases in man to 52 and 7 of these occurred in monsters. They added another case to this series, and in a footnote to their paper referred to the case described by Dahl (1937) in which, however, a traumatic or pathological basis for the defect could not be definitely excluded: their review did not include Ladd's (1936) case. The purpose of this paper is to record the findings in two additional specimens. One is of especial interest in that the defect was directly responsible for the death of the patient. Such a result has been recorded on one previous occasion only.

It is not proposed to review the literature in any detail since this has already been comprehensively covered in excellent papers by Moore (1925), de Garis (1934), and Southworth and Stevenson (1938).

REPORTS OF TWO CASES

Case 1. J. E. S., a boy, aged 2 years 2 months, was apparently healthy. He had been playing with an older boy when he complained of distress and ran to his mother holding the back of his head. He was rested, but still showed distress, and five hours after the onset refused his evening meal. A few hours later he became very restless and vomited. Fourteen hours after his first complaint, he suddenly collapsed and died. He did not receive any medical attention. An autopsy was performed eight hours after death. The body was that of a well-nourished male infant, well developed for his age. There were no external marks.

A large part of the parietal layer of the pericardial sac was absent (Fig. 1). The parietal layer present extended to enclose completely the right atrium and the greater part of the right ventricle. Anteriorly it showed a free, well-defined, constricted and rather rigid edge which crossed the sterno-costal surface of the heart from the root of the pulmonary trunk above to the inferior margin below, at a point well to the right of the apex. This free edge was situated to the right of the anterior interventricular sulcus and the interventricular branch of the left coronary artery. Inferiorly it was attached to the central tendon of the diaphragm between the inferior vena cava on the right and the line of the inferior interventricular sulcus, with its contained branch of the right coronary artery, on the left. Posteriorly it crossed the basal surface of the heart to the left of the pulmonary veins to reach again the left face of the root of the pulmonary trunk. The left ventricle and left auricle projected through this rigid orifice, the constricted edge of which had deeply grooved the surface of the heart. The mediastinal pleura on the left side below the hilum of the left lung also showed a large deficiency so that the left ventricle lay free in the left pleural cavity touching the median surface of the lower lobe of the left lung.

The surface and muscle of the right atrium were pale. The surface of the right ventricle was pale; the muscle was also pale, except at its apex, where it showed congestion and

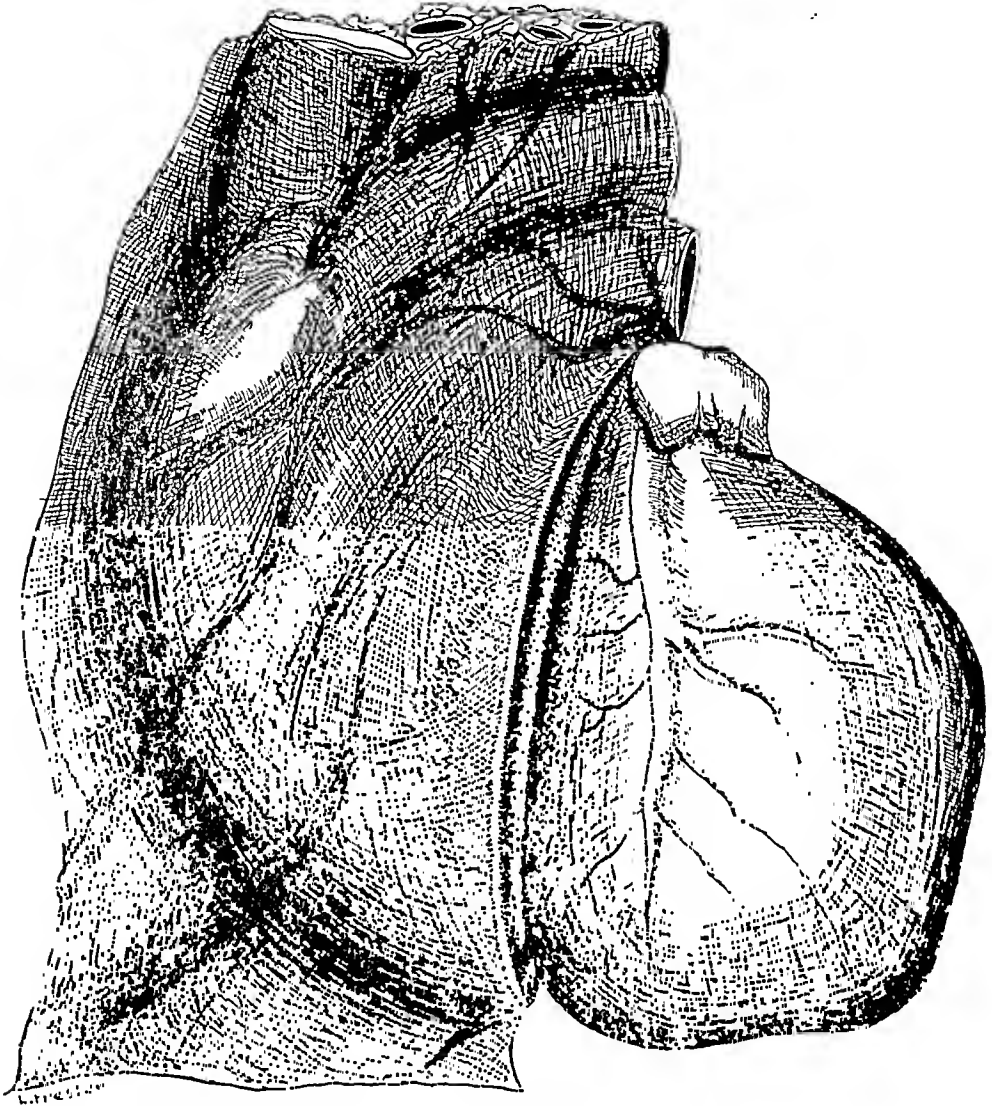


FIG. 1.—The heart and pericardium in Case 1 (see text).

hæmorrhage. The surface of the left ventricle was dark red and hæmorrhagic with many small focal hæmorrhages. The muscle of the left ventricle showed some hypertrophy. It was dark red in colour and at the base and apex there were large areas of hæmorrhage in the muscle tissue. The surface and muscle of the left atrium were very congested. The coronary sinus and great cardiac vein were distended with dark fluid blood. The cavities on the right were normal in size and contained red clot. On the left side, both the atrium and ventricle were dilated and contained red clot and fluid blood. The endocardium of the left ventricle showed some recent small hæmorrhages. The valves were normal. The foramen ovale was closed and there was no deficiency in the interventricular septum. The ductus arteriosus was patent though the lumen was constricted in the centre to about 2 mm. in diameter. The aorta and its branches were normal.

The right pleural sac and the diaphragm were normal. The lungs were large and pale-red and showed a fine œdema in all parts. The bronchi and trachea were pale and filled with fine white froth. The thymus was not enlarged and the substance was pale-red and firm. The larynx, pharynx, and thyroid were normal. The alimentary tract and peritoneum were normal and the viscera showed no congenital abnormality. The liver was moderately congested and firm. The spleen was pale-red and soft. The pancreas and suprarenals were normal. The kidneys were congested and firm. The ureters and bladder were normal. The testes had not fully descended being just below the subcutaneous inguinal ring; they showed a normal structure. The bones of the skull were normal. The membranes of the brain were congested, and the brain was rather pale and firm, but showed no abnormality.

Case 2. L. C. D., a man, aged 61 years, had had a stroke some two-and-a-half hours before admission to hospital, and could give no clear history. Examination revealed a well-nourished man showing deviation of the head and eyes to the right with tremor and flexion of the right arm and paralysis of the left arm and leg. He was treated as a case of cerebral thrombosis.

The temperature was 97.8°F. , the pulse rate 70, and the respiratory rate 20. The blood pressure was 170/100. The apex beat of the heart was in the left fifth intercostal space six inches from the mid-line. There was no right cardiac dullness and the sounds were regular and clear. Examination of the lungs and abdomen showed no abnormality. After some days moist sounds developed at the base of both lungs, and this was accompanied by elevation of the temperature and pulse rate. There was no improvement in the paralysis and the patient became incontinent. Six days after admission there was a sudden, rapid rise in the pulse rate and examination of the heart showed a "to and fro" murmur at the pulmonary area which was thought to be a friction rub. The systolic blood pressure fell to 150; the diastolic pressure remained at 100. The temperature at this stage was 100.4°F. , the pulse rate was 156, and the respiratory rate 26. The patient died eight days after admission. An autopsy was performed eight-and-a-half hours after death.

There was no pericardial sac in the true sense of the word (Fig. 2). The parietal layer was entirely deficient over most of the anterior surface of the heart, the whole of the apex, and much of the diaphragmatic and basal surfaces. It presented a free, loose margin, which was cord-like



FIG. 2.—The heart and pericardium in Case 2 (see text).

and smooth. Anteriorly the free margin appeared in the interval between the left auricle and the pulmonary trunk from which position it swung transversely to the right across the pulmonary trunk, the aorta, and the right coronary artery. It then curved downwards and crossed the sterno-costal surface of the right atrium, to the right of, and parallel to, the atrio-ventricular groove and the right coronary artery, to reach the right margin of the heart inferiorly. Turning round this margin it continued to the left, immediately anterior to the inferior vena cava, and was here attached to the central tendon of the diaphragm. It then ascended obliquely and to the left across the basal surface of the heart. On reaching the atrio-ventricular sulcus and the coronary sinus it accompanied these upwards to enter, from behind, the interval between the pulmonary trunk and the left auricle. Thus the greater portion of the heart was uncovered by parietal pericardium. Where present, this sheet was joined to the epicardium by scattered adhesions which prevented the free separation of the two structures. The parietal pleura was complete on both sides. The heart was large. It weighed 567 g. (20 oz.). There was some hypertrophy of the left ventricle.

The coronary orifices were patent. The coronary arteries were thickened and atheromatous and showed patchy calcification. All branches were grossly narrowed. The left descending branch and the middle portion of the right coronary artery were completely occluded. The epicardium, apart from adhesions, appeared normal. The muscle of the left ventricle showed coarse fibrous scarring in the inner and middle layers. The endocardium of the left ventricle was white and densely fibrous. All cavities were dilated. The papillary muscles on the left side and the interventricular septum showed fibrosis. The valves were normal. The foramen ovale and the ductus arteriosus were closed. The aorta was large, thick-walled, and markedly atheromatous.

The lungs were large and the right lung presented four well-defined lobes. There was some early bronchopneumonic consolidation at both bases. The cerebral arteries were thickened and atheromatous and the basilar artery contained some pale thrombus. The brain showed large areas of softening and necrosis in the white matter of the right hemisphere. There were numerous small hæmorrhages in both hemispheres and in the pons. The other organs were normal.

DEVELOPMENT OF THE PERICARDIAL CAVITY

The normal development of the pericardial and pleural cavities will be briefly outlined before proceeding to a discussion of the embryological basis of these defects.

During the first weeks of development, when the embryo is but 1.5–2.0 mm. in length, irregular cavities appear in the mesodermal substance of the embryo, and these, by their enlargement and coalescence, form the primitive pericardial, peritoneal, and pleural cavities. The pericardial cavity is outlined by the fusion of a series of spaces that develop in the mesoderm surrounding the endothelial anlage of the developing heart to permit the effective functioning of that organ. In the lateral mass of body mesoderm the peritoneal cavity is similarly formed about the developing gut to permit intestinal movements.

A wedge of mesoderm, directed transversely across the embryo, is left interposed between these two cavities. This is the septum transversum and it contains the developing liver and the termination of the umbilical and vitelline veins. The septum does not, however, effect a complete separation between the two cavities, for these communicate dorsally, on either side of the mid-line, by the paired longitudinally-disposed pericardio-peritoneal canals. The developing lung buds ultimately herniate into these canals which fold about them, as development proceeds, to form the pleural sacs. With the formation of the head-fold the pericardial cavity comes to lie on the ventral side of the primitive pleural sacs.

The final stages of coelomic differentiation are initiated at about the fifth week, when each pleural sac is sealed off from the pericardial cavity above and the peritoneal cavity below. Only the mechanism involved in the former process is relevant to this discussion. The separation is effected in the following manner. On each side the ductus Cuvieri establishes contact with and compresses the pericardio-peritoneal canal as it passes from the body wall

to the heart. The pressure exerted by the vessel results in the formation of an elevation, the pulmonary ridge, which narrows the lumen of the canal. The most cranial portion of this ridge of tissue is intimately related to the opening between the pleural and pericardial cavities, and here it forms a valve-like membrane, the pleuro-pericardial membrane.

Some believe that pressure exerted by the growth of the ductus Cuvieri is alone responsible for closing the communication between the two cavities, while others claim that the communication is only partially constricted by the venous channel, and that its closure is finally completed by the active enlargement of the pleuro-pericardial membrane. It is difficult to assess the respective values of these two factors in effecting the closure, but it seems certain that both operate either in succession or coincidentally. It must not, however, be forgotten that, as growth proceeds and the pericardial and pleural cavities expand, the connection between the two, being an area of inactive growth, is gradually reduced to a minute foramen. It is upon this narrowed opening that the factors indicated above operate. The following, then, may be regarded as the essential factors responsible for the closure of the communication: (1) the relative reduction in the size of the opening consequent on the more active growth of neighbouring structures; (2) the active growth within the pleuro-pericardial membrane; and (3) the continued enlargement of the pleuro-pericardial membrane under the influence of the duct of Cuvier.

INTERPRETATION OF THE DEFECTS

Few attempts appear to have been made to account for the abnormality (Keith, 1907; Perna, 1909; Risel, 1911, 1912; Plaut, 1913; McGarry, 1914; Watt, 1931; and de Garis, 1934). It is generally accepted that the defect represents a persistence of the pleuro-pericardial foramen, but opinions are divided concerning the mechanism operating to prevent its normal closure. An examination of the records shows that the condition is almost exclusively left-sided. In one monster the defect was right-sided, and in another it was thought to be bilateral. Excluding the monsters, there was one human case in which the defect was possibly on the right and Moore (1925) has described a defect on this side in the dog. The defect varies in size from a small opening to one in which the entire left side of the pericardium is absent, thereby leaving the heart and lung occupying a common serous cavity. Any explanation advanced to account for the abnormality must satisfy these morphological features.

Keith (1907) claims, on the basis of observations on two specimens, that the pericardial defect "had been produced by the lung bud growing within and expanding the communication between the pericardium and pleura, for that communication lies immediately ventral to the point at which the lung bud appears. The condition should be described as dilatation of the pleuro-pericardial foramen." Keith, however, fails to explain why the lung bud herniates into the foramen and not into its normal position, or why the defects are almost exclusively left-sided. Though such an explanation as the one offered might conceivably account for the condition in his two specimens very few of the other recorded defects could be satisfactorily accounted for in this way. Perna (1909) and later Plaut (1913) advanced the theory that persistence of the communication is the result of the arrested development of the pleuro-pericardial membrane consequent on the premature obliteration of the left duct of Cuvier. On this basis, however, all defects should be left-sided. Moore (1925) also inclines to this view though the defect which he described was on the right side.

Risel (1912) disagreed with Perna's (1909) explanation on the grounds that there were extensive combined defects in the three monsters described by him (Risel) and that in one of them the pericardial defect was bilateral. He was content to attribute the defect solely to unspecified disturbances in general coelomic differentiation occurring early in development. Such an explanation is too vague to be of value in explaining the majority of the defects recorded.

McGarry (1914) suggests that "the cells lining the coelomic space, may at some period be

particularly sensitive, and abnormal conditions occurring at this time, would result in disturbances, either an over-production or an under-production, of the serous 'derivatives' and attributes to this factor the lack of development of the pleuro-pericardial membrane. The abnormal conditions, however, are unspecified and he attempts to explain the almost exclusive incidence on the left as being due to the greater tension exerted on the pleuro-pericardial membrane by abnormal influences, induced by the asymmetry and rotation of the liver, which arrest its development. No evidence is advanced in support of this assumption.

Watt (1931) explains the defect as the result of the arrested development, from unspecified causes, of the pleuro-pericardial membrane—the subsequent enlargement of the communication being due to the presence of the heart or lung.

According to de Garis (1934) it is the heart that obstructs the closure of the foramen. He claims that the expansion of the heart tube to the left, which takes place during its enlargement and folding, is occasionally sufficiently great to prevent the pericardial, the pleural, or both these components of the pleuro-pericardial membrane, from growing forwards in their normal position. On this basis he explains all degrees of left-sided pericardial defect either with or without free communication between the pericardial and left pleural sacs. Though he cites as confirmatory evidence the fact that in many cases the heart is enlarged, elongated, or both, he maintains that "failure to find the adult heart abnormal in size or shape would not preclude the possibility that at a critical stage of development, when the pleuro-pericardial membrane grew ventrally and cranially, this growth was inhibited by the left-sided extension of the heart, which latter may or may not have been enlarged."

Thus all, with the exception of Risel, agree that the basis of the defect is obstruction of the normal development of the pleuro-pericardial membrane. Of the various theories advanced those of Perna (1909), Plaut (1913), and de Garis (1934) conform most closely to known embryological stages of development though they fail to account for those rare but confirmed cases in which the pericardium has been deficient on the right. Moreover, if the defect be attributed solely to the failure of the pleuro-pericardial membrane to develop, the pleural and pericardial cavities should remain in continuity in every case: but this is not always so. de Garis explains cases in which the pericardium alone is incomplete on the basis that the enlarging heart obstructs only the development of the pericardial aspect of the membrane.

There would appear, however, to be another factor operating in the production of these defects. The pericardium is obviously stretched as the pericardial cavity enlarges in order to accommodate the developing heart. Any opening in that enveloping sheet which is present when this process of stretching and enlargement sets in will be exaggerated unless factors normally leading to its closure operate at a much greater rate than that at which the opening is stretched. Consequently, if the foramen is to escape involvement when the pericardium is stretched it must close before the heart actively and rapidly enlarges. During the early stages of development it is conceivable that, in certain instances, the pleuro-pericardial foramen may be either unduly large, and/or its closure delayed or prevented, owing to (1) the arrested development or absence of the pleuro-pericardial membrane; (2) the failure of the membrane to grow at the rate required to close the foramen in time; (3) the absence or diminished effect of the differential growth factor which normally leads to its narrowing; or even (4) the direct influence of the enlarging heart as suggested by de Garis. Under these conditions the foramen is slowly widened as the pericardium is stretched by the enlarging heart and unless the factors responsible for its closure can, by their accelerated growth, make up lost ground it persists as a defect. Though the heart is entirely inside the pericardium in many of these abnormal cases, the defect present is obviously much larger than the original communication connecting the pericardial and pleural cavities. This lends support to the belief that the stretching to which the pericardium is subjected during development plays a significant role in maintaining and enlarging the foramen. Absence of the pleuro-pericardial membrane or obstruction to the closure of the pleuro-pericardial opening, acting singly or together, could hardly lead to an

increase in size of the original communication. If, however, the heart is unduly large, which it appears to be in approximately half the cases, then direct pressure on the foramen by the enlarged heart could assist not only in keeping it open but also in actively dilating it.

The pericardial or both aspects of the pleuro-pericardial membrane may be involved in the manner indicated, thereby imparting to the defect those varieties in which the pericardium alone is defective or in which the pericardial and pleural cavities are in continuity. Moreover, during development both the right and the left pleuro-pericardial openings may be subjected to abnormal influences of the type described, which will result in pericardial defects. Naturally, however, such abnormalities will predominate on the left since there are additional factors operating on that side (obliteration of the duct of Cuvier, enlargement of the heart to the left, etc.), which may delay or prevent the closure of the foramen until the rapid growth of the heart can influence it.

The final size of the defect is determined by the original size of the foramen, the extent to which it is stretched by the enlarging heart, and the extent to which the factors attempting to close it are successful. The size of the defect at the time when the heart first begins to enlarge will also influence the degree to which that organ will project beyond the confines of the pericardium. The defect may never, at any stage, be sufficiently large to receive any portion of the heart that continues to develop entirely within the pericardium. This latter structure then shows, when development is completed, a defect of varying size, which is never sufficiently extensive to permit the heart to herniate through it when it expands physiologically or enlarges pathologically. On the other hand the foramen may be of such dimensions in the initial stages that the heart can protrude through it either partially or entirely. Under these conditions the organ may proceed to develop outside the pericardium in a common serous cavity with the left lung. The foramen is then progressively enlarged about the heart as it develops. Again, the defect may be of such a size when development ceases that, though the heart does not normally protrude through it, it may do so in the event of any enlargement produced pathologically or under conditions of extreme stress and exertion. If the heart be driven forcibly through the aperture in this way it may be constricted by the margins in such a manner as to affect adversely cardiac efficiency—in Boxall's case and the first case reported here the constriction was sufficiently severe to cause death.

Such a theory as that outlined accounts for both right- and left-sided defects, for the overwhelming predominance of the latter, and for all types and degrees of deficiency. The factors that appear to be responsible for the defect, acting either singly or in combination, may be conveniently summarized as follows.

(1) The normal stretching of the pericardium which takes place coincidentally with the enlargement of the heart.

(2) Premature and/or abnormal enlargement of the heart which precedes the closure of the pleuro-pericardial foramen. Projection of the heart through the opening at this stage effectively prevents any possibility of closure at a later date.

(3) An abnormally large foramen which is not fully closed when the heart and pericardium start to enlarge.

(4) Delayed or non-closure of a normal pleuro-pericardial foramen which is subsequently enlarged as the pericardium stretches to accommodate the developing heart. This arrested development may be due to: (a) defective formation of the pleuro-pericardial membrane as a result of premature obliteration of the duct of Cuvier or some other unidentified influence; (b) direct obstruction by the enlarging heart; or (c) failure or diminished activity of the differential growth factor by which the connection between the pleural and pericardial cavities is gradually reduced to a minute foramen.

(5) Failure of a membrane, whose development has been delayed, to grow sufficiently rapidly to close a defect which is being slowly extended as the pericardium expands to contain the enlarging heart.

CLINICAL ASPECTS OF PERICARDIAL DEFECTS

Apart from purely embryological considerations the clinical features associated with these defects are not without interest and may be briefly reviewed.

Side. Attention has already been directed to the almost exclusive incidence on the left. Both specimens reported in this paper were left-sided.

Type. Moore (1925) has classified the reported cases into the following three groups.

Group I. Those in which the heart and left lung occupy a common serous cavity.

He records an incidence of 60 per cent in his series and Southworth and Stevenson (1938) one of 76 per cent in theirs.

Group II. Those in which there is only a foramen between the pericardial cavity and left pleural sac. He records an incidence of 21 per cent and Southworth and Stevenson (1938) one of 24 per cent. Both specimens reported in this paper would be included in this group though in the second case the defect involved the pericardium only.

Group III. Those in which there is either no trace of a pericardium or only rudiments thereof. He records an incidence of 19 per cent. Southworth and Stevenson (1938) believe that such a condition has never been conclusively demonstrated. This latter view is shared by the authors.

Associated Congenital Anomalies. Associated defects were multiple and extensive in the seven monsters. In six of the recorded series, associated anomalies in other organs were represented as follows: heart (2), lungs (1), pleural cavity (1), peritoneum (1), and kidney (1). However, as Southworth and Stevenson (1938) point out, the records of many cases are incomplete in that they contain references only to the cardiac condition. Associated defects were present in the two cases described in this report. In the first case the ductus arteriosus was patent and in the second the right lung was divided into four well-defined lobes.

Sex. From the reports that contain references to the sex it appears that the condition is approximately three times as common in males as in females. Both cases described in this report were males.

Influence on Expectation of Life. Southworth and Stevenson (1938), on the basis of a comparison of the mean age at death for the series of reported anomalies with the mean age at death for the United States area of registration for a given year, conclude that "the anomaly has no appreciable influence on life expectancy." In only two cases, that of Boxall and Case 1 in this paper, could death be attributed to the defect, and in neither was the condition diagnosed during life. Boxall's (1887) case was an adult in whom death occurred three days post-partum. Autopsy revealed a left-sided pericardial defect through which the heart had herniated and become strangulated. Death occurred suddenly with symptoms suggestive of a pulmonary embolism. It was suggested that changes in intrathoracic pressures following delivery were responsible for the fatal complication, but it is difficult to comprehend how this could have occurred three days after delivery when the heart was no longer subjected to the severe stress of labour.

Size of the Heart. From the limited number of cases containing a reference to the size of the heart, it would appear that, excluding those cases in which the enlargement was due to associated cardiovascular disease, the heart was enlarged in about 50 per cent of the cases.

Symptoms. Cardiac symptoms that could possibly be attributed to this abnormality were present in only three cases; there was a mild angina in two, while in the third adherent pericarditis was suspected during life and death was due to unexplained cardiac failure. The association between symptoms and defect in these three cases cannot, however, be regarded as conclusive. From an examination of the data contained in the case histories it may reasonably be inferred that pericardial defects are rarely the cause of cardiac symptoms. No symptoms directly attributable to the pericardial defects were present in the two cases here described.

Complications. It is interesting that in the two cases in which death could be attributed

to the abnormality death was due to herniation of the heart through the defect, this being followed by strangulation. This, however, must be considered a rare event. On occasion, when the heart is partially outside the pericardium, pressure from the firm rim of the aperture may press on one or other of the coronary vessels and obstruct it. No such factor was operating in the second case described in this report. Though the heart is enlarged in 50 per cent of the cases there is nothing to suggest that this enlargement is due to the defect. Attention has frequently been directed, however, to the fact that continuity between the pleural and pericardial cavities exposes the heart to pulmonary infection (Abbott, White, Southworth and Stevenson, and others). There was a high incidence of pleuro-pericarditis in the recorded cases, and in 27 per cent death was due to pulmonary infection complicated by pleuro-pericarditis.

Diagnosis. Ladd (1936) observed the anomaly in a child aged two during the repair of a congenital diaphragmatic hernia. Dahl's (1937) patient developed a pneumopericardium during the establishment of a left pneumothorax which, according to him, could only be explained on the basis of a defect in the pericardium. Whether this was congenital or due to disease or trauma could not be ascertained. Excluding these cases the condition has never been recognized during life though Southworth and Stevenson (1938) carried out a detailed examination and investigation of the cardiac condition in a patient who was found to have a pericardial defect post-mortem. They conclude that "although the diagnosis is probably impossible in cases where the defect is represented only by a foramen, in those where there is a common cavity on the left the diagnosis may be suspected from (1) unexplained displacement of the heart to the left, and further confirmed if, in the absence of adhesions, there is (2) abnormal mobility of the heart. Unexplained cardiac enlargement (3), if present, would be further evidence in favour of the diagnosis, though its absence would not be significant." These conclusions are in general agreement with those reported by Maude Abbott (1927).

SUMMARY

Two cases in which post-mortem examination disclosed a congenital pericardial defect have been described. In neither case was the condition diagnosed or suspected during life. In one it was directly responsible for the death of the patient.

The normal development of the pericardial cavity has been briefly outlined.

The various theories advanced to account for the defect have been discussed and the limitations of each indicated. An alternative explanation has been advanced to account for all the morphological features displayed by the defect.

The clinical features of the condition have been briefly reviewed.

REFERENCES

An extensive bibliography has not been included. Such is provided in the papers of Grant, de Garis, Moore, and Southworth and Stevenson.

- Abbott, M. (1927). Congenital Cardiac Disease, in Osler's *Modern Medicine*, Vol. 4. Philadelphia.
- Boxall, R. (1887). *Trans. Obst. Soc. Lond.*, 28, 209.
- Dahl, E. (1937). *Med. Rev. Bergen*, 54, 312.
- Grant, R. T. (1926). *Heart*, 13, 370.
- Keith, A. (1907). *J. Anat. Physiol.*, 41, 6.
- de Garis, C. F. (1934). *Anat. Rec.*, 59, 69.
- Ladd, W. E. (1936). *New Eng. J. Med.*, 214, 183.
- Moore, R. L. (1925). *Arch. Surg.*, 11, 765.
- McGarry, R. A. (1914). *Anat. Rec.*, 8, 43.
- Perna, G. (1909). *Anat. Anz.*, 35, 323.
- Plaut, M. (1913). *Z. Path.*, 12, 141.
- Risel (1911). *Dtsch. med. Wschr.*, 37, 2,405.
- (1912). *Verhandl. dtsch. path. Gesellsch.*, 15, 379.
- Southworth, H., and Stevenson, C. S. (1938). *Arch. intern. Med.*, 16, 223.
- Watt, J. C. (1931). *Arch. Surg.*, 23, 996.
- White, P. (1931). *Heart Disease*. New York.

CASUAL AND BASAL BLOOD PRESSURES

IV. THEIR RELATIONSHIP TO THE SUPPLEMENTAL PRESSURE WITH A NOTE ON STATISTICAL IMPLICATIONS

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In an article entitled *Casual and Basal Blood Pressures in Essential Hypertension* (Alam and Smirk, 1943, b), two statements were made in the discussion upon which it is desired to offer further evidence.

1. "It seems desirable to regard the casual blood pressure as made up of two parts, namely, the relatively stable basal blood pressure and a variable supplemental pressure. The supplemental pressure is the part of the casual blood pressure that is elevated as the result of the patient's physical, mental, and emotional activity, chiefly the latter; the elevation of the basal blood pressure in essential hypertension requires some other explanation." This statement that the supplemental pressure varies and the basal pressure is relatively constant refers, as is indicated in the last sentence, to the individual and not to comparisons between different individuals. Measurements of the basal pressure, whatever technique be adopted to obtain it, aim at removing these known causes of variation and at measuring a pressure that has been obtained under standard conditions of mental and physical rest. There is a high probability, therefore, that basal readings obtained under standard conditions will be more constant for the individual than casual readings taken under a variety of conditions. This has now been shown, experimentally, by Kilpatrick.

2. "The lability of the blood pressure in a case of essential hypertension may be judged by the degree of difference between the casual and basal pressures." In Fig. 4 of the paper referred to above the relationship of this difference, which we call the supplemental pressure, to the casual and basal pressures is set out graphically. It was suggested by the authors that the patients with the higher supplemental pressures are in general those with higher casual blood pressures, but their basal pressures are no higher than those of essential hypertension patients with lower supplemental pressures.

The object of the present paper is to describe some further observations that confirm the views previously expressed as to the relationship of the basal and supplemental pressures in essential hypertension, to study this relationship in health, to rediscuss the conditions under which the basal blood pressure should be measured, and to make reference to the significance which this conception has in relation to the statistical analysis of the ordinary casual (clinical) readings of the blood pressure. The opportunity is taken of referring to a comment by the editor of the *British Heart Journal* upon a statement in a previous paper (Alam and Smirk, 1943, b), which was to the effect that our results shown in Fig. 4 did not seem to support one of our conclusions.

The basal and supplemental pressures have a practical importance which should make their separate determinations a matter of clinical routine in certain classes of patient.

METHOD

Measurements of the casual and basal blood pressures were made in healthy men and in patients with essential hypertension by the method described by Alam and Smirk (1943, a).

The results together with some of those already published are analysed statistically. Experiments were made also on the effect of modifying the conditions under which the basal blood pressure is measured.

A method for determining the basal blood pressure has been recommended by committees appointed by the Cardiac Society of Great Britain and Ireland and the American Heart Association. In essence their recommendation is that the blood pressure should be measured after preparation of the subject similar to that used for basal metabolic rates. Alam and Smirk provided evidence of the need for a deliberate emotional desensitization of the subject to the presence of the observer and to the procedure of sphygmomanometry.

Observations on the relative importance of these procedures have been made as follows. Patients were fasted overnight for between 10 to 12 hours and, next morning, were transferred in their beds to a quiet, warm room where they rested for a period of half an hour. At the end of this time the observer entered, adjusted the sphygmomanometer, and measured the blood pressure. This pressure is the basal blood pressure as defined by the above-mentioned societies. The measurements of the blood pressure were then continued without intermission for a further period of half an hour in order to secure whatever additional fall of blood pressure could be obtained by the method of emotional desensitization already described.

RESULTS AND DISCUSSION

The Relationship between the Levels of the Casual, Basal, and Supplemental Blood Pressures in Healthy Males

The casual, basal, and supplemental blood pressures were measured in a number of healthy young males of European extraction and also in Egyptian males, using the method described by Alam and Smirk (1943, a). The relationship between the casual blood pressure and the supplemental pressure is set out in Fig. 1. It is seen that for the systolic pressure, higher

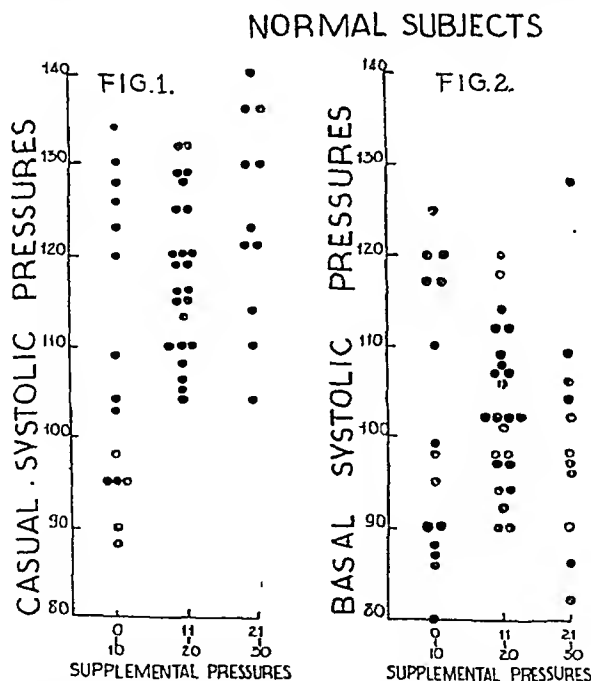


FIG. 1.—The ordinate gives the casual systolic pressure in millimetres of mercury for each of the 50 normal subjects. The subjects are arranged in three groups according to the magnitude of their supplemental (casual *minus* basal) pressures, viz. 0–10, 11–20, 21–30 millimetres of mercury. It is seen that subjects with a high supplemental systolic pressure have a better expectation of having a high casual systolic pressure.

FIG. 2.—The ordinate gives the basal systolic pressure in millimetres of mercury for the 50 normal subjects represented in Fig. 1. The subjects are arranged in three groups according to the magnitude of their supplemental (casual *minus* basal) pressures, viz. 0–10, 11–20, 21–30 millimetres of mercury. It is seen that a high supplemental systolic pressure does *not* increase the expectation of the subject having a high basal systolic pressure.

casual readings occur among patients with higher supplemental systolic pressures and lower casual readings tend to occur among patients with lower supplemental pressures. The relationship of these casual and supplemental pressures has been worked out by statistical methods and is significant, the correlation coefficient being $+0.48$. A similar relationship was found to exist between the casual and the supplemental diastolic pressures, the correlation coefficient being $+0.50$.

In Fig. 2 is set out the relationship between the supplemental and the basal systolic pressures in this same series of subjects. It is evident from the figure that when we compare the basal pressures of subjects whose supplemental pressures are high with those whose supplemental pressures are low we find the distribution of the basal pressures are much the same in the two groups. Any difference between them is not statistically significant, the correlation coefficient being -0.07 . A similar analysis has been made of the relationship between the basal and supplemental diastolic pressures and a similar absence of relationship is established, the correlation coefficient being -0.11 .

The Relationship between the Levels of the Casual, Basal, and Supplemental Blood Pressures in Patients with Essential Hypertension

In Fig. 3 is set out the relationship between the supplemental and the casual systolic pressures in a group of patients with essential hypertension. Some of the patients are those whose pressures were set out in Fig. 4 of a previous paper (Alam and Smirk, 1943, b), and the remainder are new cases. The general trend of the results is the same for the two sets. It is seen that groups of patients with higher supplemental pressures have as an average higher casual blood pressures and vice versa. The relationship between the supplemental pressures and the basal pressures for the two series of individuals is summarized in Fig. 4 of the present paper. It is found that groups of patients with hypertension selected for their high supplemental pressures do not have appreciably higher basal pressures than do groups of patients with hypertension who are selected for their low supplemental pressures. The figures when analysed statistically show no significant correlation between the heights of the supplemental systolic and of the basal systolic pressures, the correlation coefficient being -0.06 ; nor between the supplemental diastolic and basal diastolic pressures, the correlation coefficient being -0.08 .

Statistical Significance of these Results

Where C =casual blood pressure, B =basal blood pressure, and S =supplemental blood pressure: $C=B+S$.

Now it has been shown that within a uniform class of individuals, e.g. all normals or all patients with essential hypertension, the statistical expectation of an individual having a high or low value of B is not influenced by the value of S . That is to say, if from a group of individuals we select out those who have high values of B and those who have low values of B the average values of S will not differ significantly in the two groups; (shown experimentally above).

Therefore, as $C=B+S$, a group of patients selected for their higher range of basal pressures will be found to have a higher range of casual pressures. Likewise a group selected for their higher range of supplemental pressures will be found to have a higher range of casual pressures. A group selected for high values of the casual pressure will contain a preponderance of those in whom a high basal pressure happens to have coincided with a high supplemental pressure. A low casual pressure will occur when a low basal pressure coincides with a low supplemental pressure.

Now, if a random series of blood pressure readings are subdivided into groups, the first group containing the highest casual blood pressures, the second group the next highest, and so on down to the lowest group; then since $C=B+S$ and B and S are independent variables

it follows that the highest values of B and of S are associated together in the first group and the lowest values associated in the lowest group. In the middle groups both B and S cover a wide range, but the average B and the average S are both of intermediate magnitude.

This way of arranging results inevitably brings about a juxtaposition of high basal with high supplemental pressures and of low basal with low supplemental pressures. The juxtaposition has been pre-determined by the ordering of results in descending order of magnitude

ESSENTIAL HYPERTENSION CASES

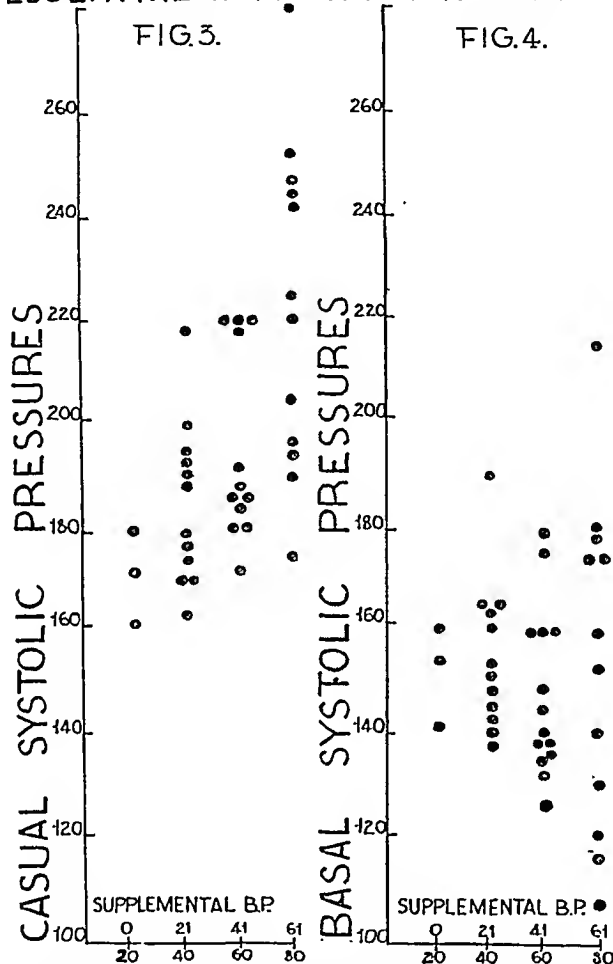


FIG. 3.—The ordinate gives the casual systolic pressures in millimetres of mercury for each of the 39 hypertensive subjects. The subjects are arranged in four groups according to the magnitude of their supplemental (casual *minus* basal) pressures, viz. 0-20, 21-40, 41-60, 61-80 millimetres of mercury. It is seen that subjects with a high supplemental systolic pressure are more likely to have a high casual systolic pressure.

FIG. 4.—The ordinate gives the basal systolic pressures in millimetres of mercury for the 39 hypertensive subjects represented in Fig. 3. The subjects are arranged in four groups according to the magnitude of their supplemental (casual *minus* basal) pressures, viz. 0-20, 21-40, 41-60, 61-80 millimetres of mercury. It is seen that a high supplemental systolic pressure does *not* increase the expectation of the subject having a high basal systolic pressure.

of the casual blood pressure and the juxtaposition has no biological significance whatsoever. This somewhat inconspicuous error in selection is apt to lead to rather fundamental differences in the conclusion drawn.

Let us consider the following purely numerical example. Take the following 12 values of B: 120 120, 130 130, 140 140, 150 150, 160 160, 170 170; now let the values of S be 20 for one and 60 for the other of these paired values of B. Thus, in our artificial example, the distribution of the values of S does not bear any relation to the value of B 20 60, 20 60, 20 60, 20 60, 20 60, the values of C being equal to $B+S$ are as follows: 140 180, 150 190, 160 200, 170 210, 180 220, 190 230. Arrange these results in order of magnitude of C:

| C | B | S | C | B | S | C | B | S |
|-----|-----|----|-----|-----|----|-----|-----|----|
| 230 | 170 | 60 | 190 | 170 | 20 | 170 | 150 | 20 |
| 220 | 160 | 60 | 190 | 130 | 60 | 160 | 140 | 20 |
| 210 | 150 | 60 | 180 | 160 | 20 | 150 | 130 | 20 |
| 200 | 140 | 60 | 180 | 120 | 60 | 140 | 120 | 20 |

Average the 4 highest, 4 middle, and 4 lowest values of the table and we obtain:

| | C | B | S |
|--------------------|-----|-----|----|
| High group | 215 | 155 | 60 |
| Middle group | 185 | 145 | 40 |
| Low group | 155 | 135 | 20 |

Thus we have a series of averages in which casual, basal, and supplemental pressures show parallel variations.

It is very tempting from such an analysis to draw the conclusion which was drawn by the editor of the *British Heart Journal*, from a similar analysis which he made, in commenting upon a previous publication of Alam and Smirk, namely, that there is a relationship between the levels of the basal and supplemental pressures. This relationship, however, does not exist, the figures in the numerical example being so chosen that there should be no such relationship. It follows, therefore, that this statistical method as used by the editor is inapplicable. The parallel increase in the values of basal and supplemental pressures in the above table and in that published by the editor in his comment are the result of using a method of selection which pre-determined the final result.*

Mr. Williams, statistician to the economics department of the Otago University, has been kind enough to work out for me the correlation coefficients of various relationships.

TABLE I
VALUES OF CORRELATION COEFFICIENTS

| | No. of cases | Correlation coefficients | | | Squares of coefficients | |
|------------------------------|--------------|--------------------------|------|-------|-------------------------|-------------------|
| | | Rbc | Rcs | Rbs | R ² bc | R ² cs |
| Normal systolic | 50 | 0.84 | 0.48 | -0.07 | 0.71 | 0.23 |
| Normal diastolic | 54 | 0.77 | 0.50 | -0.11 | 0.59 | 0.25 |
| Hypertensive systolic | 39 | 0.75 | 0.61 | -0.06 | 0.56 | 0.37 |
| Hypertensive diastolic | 37 | 0.75 | 0.59 | -0.08 | 0.56 | 0.35 |

In the above table Rbc represents the relationship between basal and casual pressures, Rcs the relationship between casual and supplemental pressures, and Rbs the relationship between basal and supplemental pressures.

With normal pressures, systolic and diastolic, and hypertensive pressures, systolic and diastolic, the expectation is that individuals with the higher basal pressures are more likely to have high casual pressures and vice versa: The chance of the blood pressure figures, upon which these relationships are based, occurring by coincidence are less than 1/100,000 for each of the above four groups and taking all four sets together the chances of the relationship being coincidental must be less than one in ten million. There is also a direct correlation between the height of the supplemental pressures and the expectation of high casual pressures in all four groups. The chance of this happening by coincidence in the normal groups is less than 1/50,000 for each group and for the hypertensive groups is less than 1/100,000. Taking the four groups together the chance of coincidence is quite negligible.

Within the four groups studied, however, basal and supplemental pressures are independent

* "I am glad to publish this paper especially because it appeared to me that Fig. 4 of the paper by Alam and Smirk (1943, b) did not convincingly show that the basal and the supplemental pressures were independent variables. The further statistical analysis submitted in this present paper, however, seems conclusive evidence that this is so."—EDITOR.

variables. That is to say, in none of the four groups does possession of a high or low supplemental pressure increase or diminish appreciably the expectation of a high basal pressure. While the view is expressed that the basal blood pressure is an independent variable when we compare the different members of a *group* of individuals, yet this statement is in no way inconsistent with the view expressed earlier that, in the absence of any marked physiological change, the basal blood pressure of an *individual* is relatively constant for that individual.

The squares of the correlation coefficients for the relationship of casual to supplemental pressure are appreciably higher for the hypertensive groups (systolic and diastolic) than for the normal group (systolic and diastolic). This indicates that the supplemental pressure forms a significantly higher proportion of the casual pressure among the hypertensive than among the normal group.

Improvements in the Method of Measuring the Basal Blood Pressure

A comparison has been made in a series of 13 subjects of the level of the basal blood pressure. (1) Determined by the method recommended by the committees of British and American cardiologists; in essence this consists of preparation of the patient in the manner laid down for basal metabolic rates prior to the measurement of the blood pressure. (2) Immediately after this measurement the procedure of emotional desensitization recommended by Alam and Smirk, 1943, a, was applied with the object of determining whether this additional procedure caused a further decrease in the level of the blood pressure. (3) The patient then had breakfast, assumed normal ward life, and later on in the day returned for the measurement of the basal blood pressure by the procedure recommended by Alam and Smirk. That is to say the procedure of emotional desensitization was carried out without having the patient in the basal metabolic state.

The results are set out in Table I. It will be seen that rest and emotional desensitization produce blood pressures which are similar to those obtained by the procedure recommended by the committees of British and American cardiologists. The combination of the two procedures, however, appears to give still lower values for the basal blood pressure than the use of either separately. It seems improbable that much lower values of the basal blood pressure will be obtained by other procedures, but it is not unlikely that minor improvements can be effected.

TABLE II
COMPARISON OF METHODS OF MEASURING BASAL BLOOD PRESSURE

| Subject | Casual blood pressure | Basal blood pressure by three methods | | |
|------------|-----------------------|---------------------------------------|-------------------------------------|----------------------------|
| | | Method of cardio-logical committees | Method of emotional desensitization | Combination of two methods |
| D | 192/118 | 188/100 | 182/124 | 164/98 |
| C | 122/86 | 122/86 | 110/79 | 106/68 |
| J | 118/54 | 96/58 | 106/52 | 92/54 |
| McN | 98/66 | 106/64 | 94/75 | 96/60 |
| Mu | 130/74 | 132/76 | 110/77 | 122/74 |
| Mo | 104/74 | 98/62 | 94/64 | 80/62 |
| S | 134/90 | 130/90 | 112/80 | 128/88 |
| Wi | 122/66 | 128/68 | 118/55 | 124/66 |
| Ma | 114/78 | 106/78 | 110/76 | 92/78 |
| N | 120/60 | 106/70 | 110/58 | 94/61 |
| O | 122/68 | 112/68 | 116/58 | 110/65 |
| W | 130/76 | 114/74 | 116/68 | 112/70 |
| Me | 116/72 | 92/60 | 106/68 | 90/65 |
| Average .. | 124.8/75.5 | 117.7/73.4 | 114.2/71.8 | 108.5/69.9 |

SUMMARY

The casual blood pressure may be regarded as the sum of the basal blood pressure and the supplemental pressure; this last represents the degree of blood pressure elevation above the basal level due to whatever degree of physical, emotional, and supra-basal metabolic activity is present at the time of blood pressure measurement. The basal pressure is the pressure measured at a time when physical, emotional, and metabolic activity are reduced to a physiological minimum. In cases where it is impossible to do this because of restlessness or emotional tension, the reading obtained should not be described as basal. Failure to obtain the true basal reading will not always be apparent to the observer especially when, as is most commonly the case, the failure is due to emotional reasons.

Both normal and hypertensive subjects with a high basal pressure have a greater statistical expectation of having a high casual pressure than do those whose basal pressure is low. Likewise those with high supplemental pressures have a greater statistical expectation of a high casual pressure than do those whose supplemental pressure is low.

In comparing one individual with another the basal and supplemental pressures on the other hand are independent variables in the sense that the level of the basal blood pressure in an individual is no guide to the probable level of the supplemental pressure.

Most statistics concerning the level of the blood pressure are concerned with the casual readings. The fact that when comparing one individual with another, within a comparable physiological group, the casual blood pressure is to be regarded as the sum of two independent variables has statistical implications which are discussed.

The supplemental pressure forms a significantly higher proportion of the casual pressure among patients with essential hypertension than among normal subjects.

An improved method is recommended for determining the basal blood pressure.

I wish to express my thanks to Miss Fulton for technical assistance.

REFERENCES

- Alam, M., and Smirk, F. H. (1943, a). *Brit. Heart J.*, 5, 152.
— (1943, b). *Ibid.*, 5, 156.
Kilpatrick, J. A. Personal communication.

MYOCARDIAL INFARCTION

BY

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Owing to postal delays caused by the authors' movements, this summary of their recent paper (British Heart J., 6, 115-128, 1944) was not received in time to print with the paper. The opportunity is taken of adding one sentence and correcting two misprints.—EDITOR.

Any discussion of myocardial infarction should correlate the pathological changes with the anatomical structure of the heart. In this paper a review of the anatomy of the cardiac muscles and of the coronary arterial tree and the diseases thereof that may lead to muscle infarction is given. The consequences of interference with the blood flow in this tree are discussed.

The ventricular and auricular (atrial) walls are composed of several muscles, which are in reality as distinct as the three glutei muscles making up the gluteal mass. The separation of these muscles was first shown by anatomical dissection, and has been confirmed by the demonstration of independent blood supplies, and their individual involvement in various pathological states.

Anastomotic channels of arterial size between major coronary arteries exist of all ages. Pressure difference between the ends of any vessel is the factor which determines the direction of blood flow in that vessel. In a normal coronary circulation arterial anastomoses will have approximately the same pressure at either end, so that the blood supply will be small and may easily change in direction from time to time. In hearts the seat of obstructive arterial changes, marked difference of pressure between the ends of the anastomotic channels may easily occur, and then these vessels enlarge and become visible to the naked eye. The distribution of fields of supply will also become upset and it will then be impossible to predict the field of supply of any one of the major coronary arteries.

No one arterial branch supplies the whole of any one ventricular muscle. It is important that the parent artery, which gives branches to the pericardial portion of a superficial muscle, gives branches also to the endocardial portion of that muscle, but not to the deep branches in between.

No essential difference exists between diseases of the arteries of the heart and those of other organs of the body. Regardless of which portion of the coronary tree is affected, the gravity of the lesion is largely determined by the degree of vascular obstruction. In most cases thrombosis is secondary to underlying vascular disease, and primary thrombosis of the coronary arteries has not been encountered. A discussion of the various diseases of the coronary arteries follows. The importance of arteriosclerotic intimal hæmorrhage in precipitating thrombosis and vascular occlusion is stressed. Similar hæmorrhages in the media lead to dissecting aneurysm.

Myocardial ischæmia is discussed under the following headings: (1) infarction of the ventricular wall; (2) interference with ventricular function; (3) rupture of the ventricle; (4) ventricular aneurysms; (5) infarction of the atrial wall; and (6) electrocardiographic changes. The effects of sudden and gradual occlusion in normal and diseased coronary

arteries are considered. The resulting infarcts may involve parts of several muscles (whole thickness of ventricular wall), or may be confined to a portion of one muscle, or may form scattered small foci.

Interference with ventricular function may result either from an inability of the ischæmic heart adequately to expel blood or from the development of abnormal rhythms.

The physical basis of aneurysm formation is the same in both ventricle and aorta, for in both places muscle tissue is active in withstanding pressure, and when enough of it is destroyed and replaced by collagen, gradual stretching and sac formation occurs. Two types of ventricular aneurysms are described. Basal aneurysms show two laminar scars indicating that destruction of two deep muscles is essential to their formation. Apical aneurysms, in contrast, show a single laminar scar due to the involvement of the superficial musculature.

The principles outlined in discussing ventricular infarcts are strictly applicable to those occurring in the walls of the auricles. Auricular infarcts occur in about 17 per cent of cases of ventricular infarction and usually involve the right auricular appendage. Disturbance in auricular electrical activity in such cases may suggest damage of the auricular muscles, possibly due to infarction.

The paper concludes with a brief discussion of the limitations of electrocardiographic changes.

ERRATA

Page 119.

Line 6. *Insert* " In most cases thrombosis is secondary to underlying vascular disease, and hence may complicate any of the lesions described below. We have not encountered primary thrombosis of the coronary arteries."

Line 16. *Insert* " by " between " muscle " and " fibrous tissue."

Line 19. *Insert* " 20 " for " 10 " before per cent.

CORRECTED REFERENCES

Flett, R. L. (1927). *J. Anat.*, 62, 439.

Wartman, W. B. (1933). *Amer. J. med. Sci.*, 197, 7.

— (1940). *American Association for the Advancement of Science*, Publication 13.

A CASE OF TUBERCULOUS PERICARDITIS

BY

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Received October 21, 1944

Uncomplicated tuberculous pericarditis is not common, and this case is described because it gives a good picture of the march of the disease both clinically and pathologically.

DESCRIPTION OF CASE

A man, aged 22, who worked as a shop assistant, was admitted to Addenbrooke's Hospital on March 11, 1943, with the following history. About mid-February he first began to feel generally out of sorts and over the space of a few days developed a dry, irritating cough which kept him awake at night, a dull pain over the præcordium, nausea, weakness, and slight breathlessness on exertion. These symptoms persisted until his admission.

His previous health had been good and the only illness he remembered was an attack of "pleurodynia" at the age of 18. His family history was healthy with no tuberculosis.

On admission the heart was greatly enlarged both to left and right, the apex beat could not be seen or felt, the sounds were faint and tic-tac in quality, the pulse small, regular, and rapid (110), the respiratory rate 22, the temperature intermittent and rising to 100 or 101, and the blood pressure 110/80.

The most arresting physical sign was a loud rub audible over the whole pericardium but most marked at the base.

The cardiogram showed low voltage curves with inversion of T in leads I, II, IVR, and IVF (Fig. 1) and X-ray showed the typical shadow of a large pericardial effusion (m.t.d. 17 cm.; see Fig. 2). The sedimentation rate (Westergren) was 60 mm. in one hour.

Progress. Except for a period of two months in September and October when he rested at home, he remained under observation in hospital until his death on December 9.

The progress of the disease appeared to fall into three clinical phases.

- (1) The phase of increasing effusion leading to congestive failure (4 months).
- (2) The phase of decreasing effusion with temporary recovery (3 months).
- (3) The phase of increasing thickening and fibrosis of the pericardium and congestive failure ending in death (3 months).

Phase 1. During this phase the rub disappeared, there was a progressive increase in the size of the effusion and the temperature fell gradually to normal in six weeks. In the first few weeks the blood pressure fell to an average of 90/65 at which level it remained for about three months and the veins of the neck became distended and remained so. This phase culminated in an attack of congestive failure with a large pleural effusion at the right base, some ascites and slight general oedema.

Phase 2. Following recovery from the congestive failure (Fig. 3) the pericardial effusion began to subside gradually and there was marked general improvement with a steady rise of blood pressure to an average level of 110/80 and lessening venous distension. By the end of July his resting pulse rate was 80-100, and he appeared to

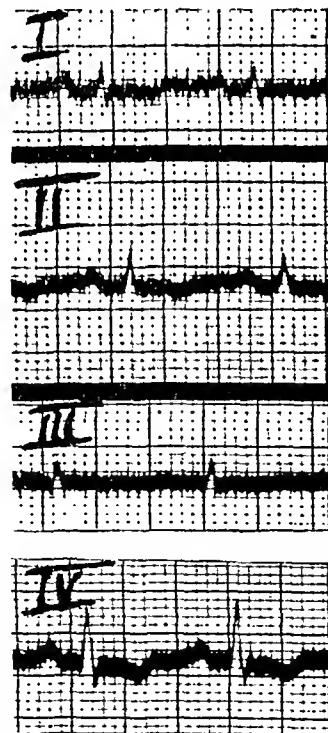


FIG. 1.—Cardiogram (25/4/43) showing P-R 0.16 sec. and inversion of T waves.



FIG. 6.—Photograph of the heart showing a thickened and distended pericardium beset with granulomatous plaques.

atheroma of aorta, its abdominal part being rather narrower than the average but within normal limits. No excessive atheroma of pulmonary arteries. Non-specific inflammatory changes only in several moderately enlarged lymph glands on the outer surface of the pericardium near the hilum of the left lung. Ill-defined firm greyish areas suggesting granulomatous tuberculosis in several lymph glands on the left posterior aspect of the pericardium. Caseous tuberculosis of one small mediastinal lymph gland near the left bronchus, between the main left pulmonary artery and the arch of the aorta; this gland was about 1.5 cm. from the pericardium at its nearest point, and its soft crumbling centre surrounded by a dense zone of fibrosis. Small (0.2 cm. diam.) calcareous nodule surrounded by fibrous tissue in upper lobe of left lung near apex. Both lungs partially collapsed by pleural effusions and slightly congested. Clear yellowish fluid in serous cavities: right pleura 1870 c.c., left pleura 920 c.c., peritoneum 2640 c.c. Mesenteric lymph glands rather large but normal in appearance. Changes in the other organs were those of chronic venous congestion. Heart not weighed because preserved with pericardium for mounting.

Microscopic. Heart. Chronic tuberculous pericarditis with much increase of fibrous tissue. No definite lesions in myocardium. *Lymph glands* (from posterior surface of peri-

cardium). Typical granulomatous tuberculosis with abundant giant cells but no caseation. *Inferior vena cava*. Conspicuous thickening of wall. *Mesenteric lymph gland*. Very wide but almost empty sinuses and atrophy of lymphoid tissue; no tuberculosis.

The changes in the other organs were those of chronic venous congestion.

Bacteriological. By guinea-pig inoculation with pericardial fluid tubercle bacilli of eugonic human type were demonstrated.

THE MECHANISM OF IMPAIRMENT OF CARDIAC FUNCTION

During the necropsy a somewhat crude attempt was made to determine whether the pericardial effusion itself at the time of death was likely to have caused any serious impairment of cardiac function.

Presumably such impairment would be mainly due to limitation of the intake of blood into the auricles during diastole. If $V(e)$ = the volume of the effusion, $V(b)$ = the total volume of blood that enters and is expelled from the heart at each beat, and $V(h)$ = the volume of the substance of the heart itself, then impairment of cardiac function due to an effusion will not be expected unless $V(e) + V(b) + V(h)$ is sufficiently great to stretch the parietal pericardium so that before the end of diastole the pressure inside the pericardium (and hence in the auricles) becomes equal to that in the venæ cavæ. $V(b)$ will then be reduced and the function of the heart impaired. We attempted at necropsy to discover whether this critical volume had been attained by measuring the relationship between known increases in the total volume of the pericardial contents and the intra-pericardial pressure.

When the thorax and abdomen had been opened, and before any further dissection, the superior and inferior venæ cavæ were ligatured immediately above and below the intact pericardium. This was done in order to prevent alterations in the volume of the pericardial contents due to blood being squeezed out of the heart during the subsequent manipulations. A glass funnel was attached to one end of a length of rubber tubing and a blood transfusion "taking" needle to the other end. The needle was then inserted into the pericardium (through the diaphragm, to minimize leakage) and 35 c.c. pericardial fluid was allowed to escape through the tube into a bottle. This sample was reserved for examination, but the original volume of the effusion was restored by pouring 35 c.c. water back through the funnel into the pericardial sac. The funnel was now held in such a position that a mark on its stem was 10 cm. above the pericardium and water was poured in until the level remained stationary at the mark. The volume of water that had been added was noted, and the funnel was then raised until the mark was 20 cm. above the pericardium. The process was then repeated; and similarly with the level at 30 cm., and 50 cm. The same measurements were made on another subject whose heart and pericardium appeared normal. The results were as follows:

| Intra-pericardial pressure (cm. water) | Volume of fluid introduced into pericardium (c.c.) | |
|---|--|---------|
| | Patient | Control |
| 10 | 140 | 260 |
| 20 | 180 | 285 |
| 30 | 215 | 305 |
| 40 | 235 | 312 |
| 50 | 260 | 330 |

Strictly, in comparing these measurements, allowance should be made for the volume of blood and clot present in the chambers of each heart, but it was not found possible to measure this volume accurately without spoiling the heart as a museum specimen, and this we were loath to do. However, the volume of the contents was relatively small (less than 50 c.c.) in each of the hearts and there was no great inequality in the amounts.

These results suggest that an effective venous pressure of 10 cm. water should have enabled the heart to deal with at least 140 c.c. blood at each beat if its action were hampered only by the mechanical effects of the effusion. The average systolic output of normal adults at rest

is between 60 and 70 c.c. (Grollman, 1932), but this figure is the output of one ventricle only: the total output of the heart is 120–140 c.c. per beat. Thus it seems that in spite of the effusion the patient should have been able to maintain a normal cardiac output while resting, provided that his effective venous pressure was not less than 10 cm. water. His actual venous pressure was not measured, but the conspicuous venous engorgement observed during life and the thickening of the wall of the inferior vena cava seen at necropsy suggest that the pressure was probably greater than this, and hence that the impairment of cardiac function about the time of death was not due to the mechanical effects of the effusion.

Of other possible causes of impairment of cardiac function, the greatly increased thickness and rigidity of the visceral pericardium appears the most likely. There was little histological evidence of myocardial damage although this had been indicated by the prolonged P–R interval of the cardiogram. Constriction of the vessels entering the heart was excluded.

SUMMARY

This patient's initial tuberculous infection was situated near the apex of the left lung and was very small. The infection apparently spread from the lung to a mediastinal lymph gland between the left bronchus and the pericardium, and from this gland to the pericardium—though no definite track of infection between the gland and the pericardium was in fact found at necropsy. Tuberculous pericarditis with effusion followed, and death was due to congestive heart failure. There was no evidence of tuberculosis elsewhere in the body. Evidence is given which suggests that at the time of death the pericardial effusion played a relatively small part in limiting cardiac efficiency, and it is suggested that increased thickness of the visceral pericardium with loss of its pliability was the chief cause.

We wish to thank Dr. J. F. Gaskell for permission to investigate and publish this case, Dr. C. H. Whittle for some of the pathological investigations, and Dr. Ff. Roberts for the X-ray examinations.

REFERENCES

- Grollman, A. (1932). *The Cardiac Output of Man in Health and Disease*, London.
Suzman, S. *Brit. Heart J.*, 5, 19.

PERFORATION OF THE INTERVENTRICULAR SEPTUM DUE TO CARDIAC INFARCTION

BY

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From the Harrogate General Hospital

Received August 10, 1944

Until December 1943 thirty-eight cases of rupture of the interventricular septum have been reported; of these eight were diagnosed ante-mortem. Rupture of the septum usually occurs in the seventh and eighth decades in patients who have had long-standing high blood pressure. It is more common in first infarctions, where the infarct is small and the blood pressure remains above 160/100 after infarction. The average time of rupture is between the third and twelfth days (Edmunson and Hoxie, 1942).

Stanley (1937) reported that, at the time of rupture of the septum, his patient complained of sudden substernal pain and became shocked. After rupture a systolic murmur, which may be rough or blowing, has been noticed over the sternum in the fourth and fifth interspaces in all reported cases, generally accompanied by a systolic thrill (Sagar, 1934). In all cases observed within two or three hours of rupture there has been cyanosis and dyspnoea and usually there has been some degree of congestive failure throughout the illness; death usually being due to right ventricle failure (Bayley and Fader, 1941).

Although most reported cases have died during the first week after perforation of the septum, diminution of the congestive failure has followed prolonged use of mercurial diuretics (Wood and Livezey, 1942) and digitalis therapy (Leonard and Daniels, 1938).

Seven cases have been reported that lived for more than four weeks, of which Moulton (1942) mentions four. The longest recorded duration of life after perforation is four years and ten months (Wood and Livezey, 1942). Gross and Schwartz (1936) record a case which survived two months and Stanley (1937) one which lived five months.

CASE REPORT

E. M. V., a woman aged 69 years, was admitted to hospital on 27/10/43. She had been known to have high blood pressure for the preceding year. For fourteen months before admission she had complained of aching across the shoulders and down both arms, occurring on exertion and immediately relieved by rest. On 17/10/43, ten days before admission, she had an acute attack of pain in the shoulders and down both arms, which came on at rest. The pain lasted about an hour, and was followed by a feeling of faintness. After the attack she became increasingly dyspnoeic on exertion, but there was no recurrence of the pain.

On admission to hospital she was not cyanosed and there was no dyspnoea at rest. The pulse was regular at a rate of 120. The blood pressure was 100/70. The apex beat was four and a half inches to the left in the fifth interspace and was diffuse and moderately heaving. A thrill was not felt. A blowing systolic murmur was heard over the lower sternum, replacing both sounds in this area; it was conducted towards the axilla and up the sternum. There was slight oedema over the sacrum. The veins of the neck were not distended and the liver was not palpable. Crepitations were heard at both pulmonary bases.

A cardiogram (Fig. 1) showed evidence of recent posterior infarction. A radiogram showed cardiac enlargement to the right and left, and basal pulmonary congestion. The white count was 15,000, of which 68 per cent were polymorphonuclear. The blood urea was 55 mg. per 100 c.c. of blood. Urine analysis showed a trace of albumin, an occasional erythrocyte, and a few leucocytes. The blood sedimentation rate was 14 (Wintrobe).

She was treated with ammon. chlor., grains 30, and with neptal, 2 c.c. intramuscularly every third day, which produced a moderate diuresis, and later with cardophylin intravenously and by mouth, to which she showed no response.

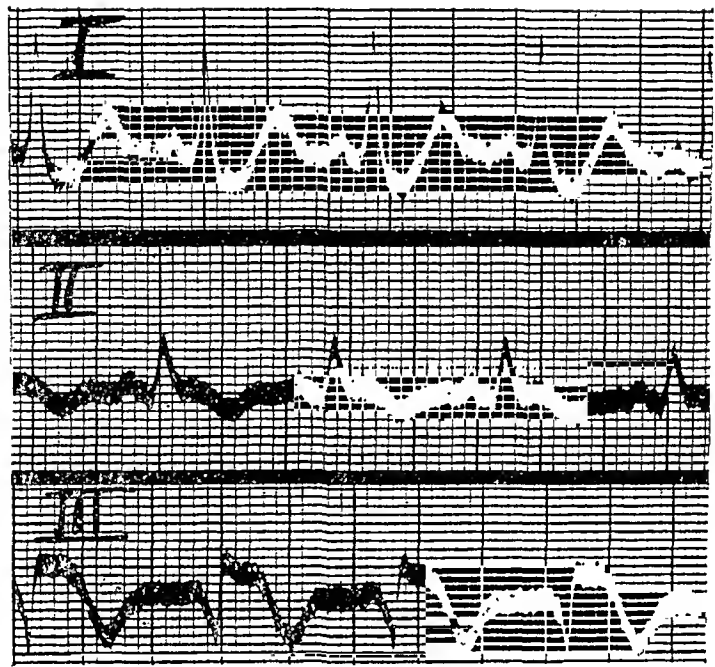


FIG. 1.—Electrocardiogram with evidence of posterior infarction—depression of the S-T junction in lead I, and bowed inversion of T in leads II and III.

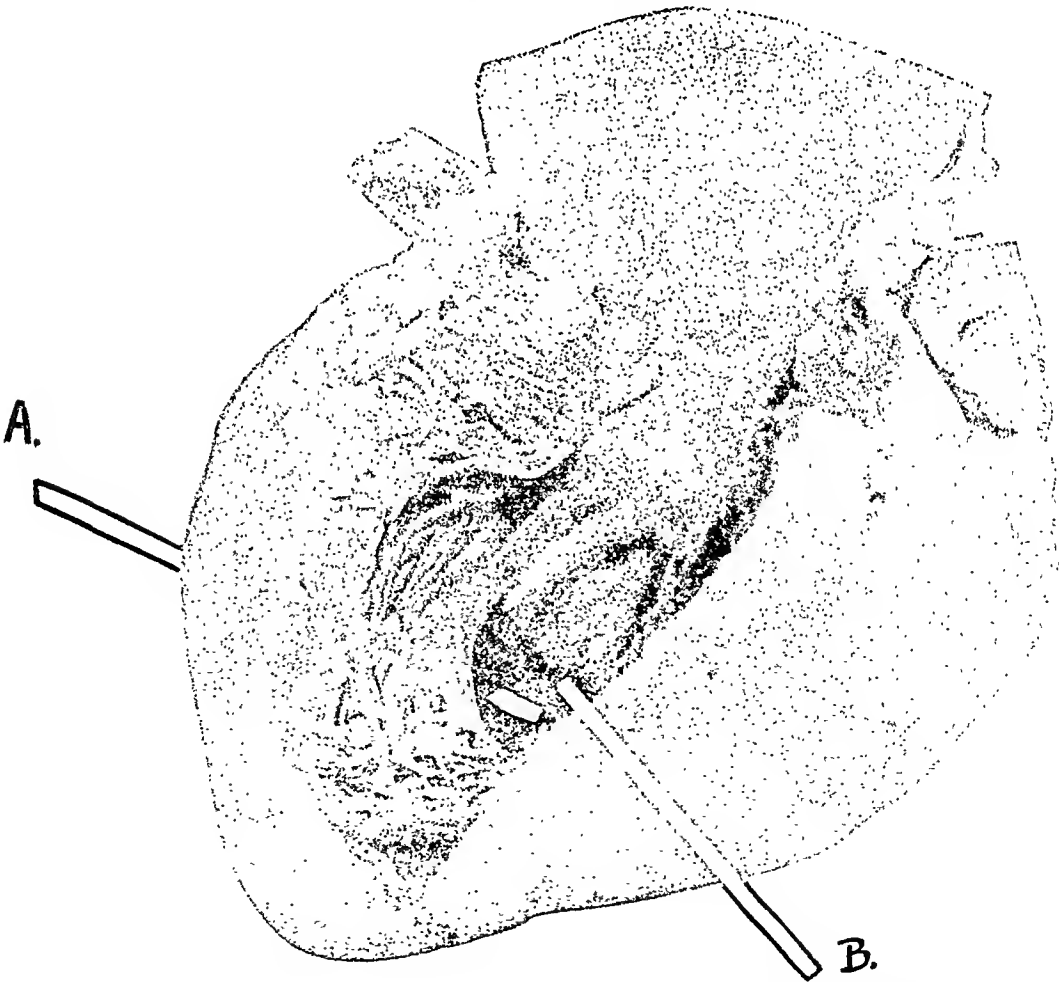


FIG. 2.—Photograph of heart showing perforation of interventricular septum. (A) Perforation in the inter-ventricular septum. (B) Aneurysmal dilatation seen from the left ventricle.

The heart sounds remained constant and there was no noticeable increase in the heart size. A cardiogram taken after four weeks continued to show signs of infarction but no other abnormality. The pulse rate was persistently rather rapid, varying between 88 and 124. Crepitations persisted at the pulmonary bases throughout her illness but the sacral œdema rapidly disappeared. There was no further development of congestive failure, though the patient frequently complained of nausea and vomited occasionally.

The patient lived for five weeks after admission to hospital, during which time her general condition improved slowly until two hours before death, when she complained of gradually increasing præcordial pain with nausea and faintness. She became collapsed and her blood pressure fell. This was considered to be due to further cardiac infarction.

Post-mortem findings. (Dr. S. Wray). The heart weighed approximately 400 g. and showed slight general enlargement. The thickness of the left ventricle was 18 mm. (normal 6–12 mm.), and of the right, 9 mm. (normal 3.2 mm.).

The lumen of the right coronary artery was almost obliterated by old thrombus but was just patent. The posterior part of the left ventricle and the posterior part of the interventricular septum showed ischæmic changes due to an infarction of some weeks duration. In the posterior part of the septum, including the membranous septum, there was an aneurysmal dilatation extending into the right ventricle. The base was 30 x 20 mm. in area, and it was 15 mm. deep. At its apex there was a slit-like perforation, 10 mm. long, giving free communication between the ventricles. The walls of the aneurysmal sac, and of the perforation, at its apex, were smooth, suggesting that the lesion was of some weeks duration. There was nothing to suggest that the lesion was of congenital origin. (Fig. 2). The part of the endocardium of the right ventricle immediately opposite the perforation showed a thickened area, whiter than the surrounding tissue.

The descending branch of the left coronary artery was completely occluded in its upper part by an atheromatous plaque and super-added recent thrombosis. The myocardium of the anterior part of the left ventricle showed very recent infarction.

The valves of the heart were normal. The right pleural cavity contained about half a pint of clear yellow fluid. The lungs showed basal œdema only. The liver was normal in size, but of mild nutmeg appearance.

DISCUSSION

Before death the diagnosis made with some confidence was a rupture of the interventricular septum following posterior cardiac infarction. The diagnosis was based on the recent development of a systolic murmur beneath the sternum, following a single cardiac infarction, in a patient who was known to have had high blood pressure.

The signs were not typical of the condition as it has been previously described, as there was no history of any initial shock, no systolic thrill, and the systolic murmur was blowing rather than rough. These atypical findings may be due to the fact that the infarcted septal area was first stretched to form an aneurysmal dilatation, and only later became sufficiently thin to perforate. In this case the perforation might occur slowly, so that there would be no initial shock. The absence of thrill might be due to a slow rate of blood flow through the perforation because of the presence of the aneurysm. Compensation for the abnormal circulation was established by the relative hypertrophy of the right ventricle. This explains the absence of marked congestive failure.

The effects of perforation of the interventricular septum in this case were a rapid pulse rate and persistent basal pulmonary œdema.

SUMMARY

A case of rupture of the interventricular septum, accompanied by an aneurysmal dilatation of the septum is described. The signs were not typical. An explanation of the atypical findings is attempted.

I wish to thank Dr. C. W. Curtis Bain for his interest and help.

REFERENCES

- Bayley, R. H. and Fader, D. E. (1941). *Amer. Heart J.*, 21, 238.
- Edmunson, H. N. and Hoxie, H. J. (1942). *Ibid.*, 24, 719.
- Gross, H. and Schwartz, S. P. (1936). *Ibid.*, 11, 626.
- Moulten, S. E. (1942). *Arch. intern. Med.*, 69, 108.
- Sager, R. V. (1934). *Ibid.*, 53, 140.
- Stanley, D. F. (1937). *Amer. Heart J.*, 14, 420.
- Wood, F. C. and Livezey, M. M. (1942). *Ibid.*, 24, 807.

CARDIO-AORTIC FISTULA

BY

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A diastolic murmur heard along the right border of the sternum is regarded as evidence of aortic incompetence, but to this general rule of auscultation there is one exception, and this was present in the case reported here.

A labourer, aged 54, was admitted to the London Hospital with breathlessness and swelling of the legs. He had been quite well until two weeks before admission, when he complained of abdominal pain, vomiting, and great breathlessness. He attributed all his symptoms to indigestion. The pain and vomiting ceased after an hour, but breathlessness recurred on slight exertion. Occasionally effort induced a heavy retrosternal pain which radiated down the right arm. One week before admission he noticed swelling of his ankles. He had a slight cough but there was no sputum. His sleep had been disturbed by attacks of breathlessness. He had never had rheumatic fever nor syphilis; and he had been accustomed to heavy manual work all his life.

On admission he was orthopnœic, but cheerful and cooperative. He was pale and anæmic (hæmoglobin, 56 per cent). The pulse was irregular from auricular fibrillation and rapid (132 a minute). The blood pressure was 115/70. There was venous engorgement in the neck and prominent venous and arterial pulsation. A systolic thrill was felt over the carotid arteries. The apex beat was displaced as far as the anterior axillary line in the sixth intercostal space. The first and second heart sounds were heard over the apex and a third heart sound had been added. A harsh systolic murmur was audible all over the heart, but it was loudest in the aortic area: when the heart rate was slowed to 90 a systolic thrill was felt in the aortic area and a soft diastolic murmur became distinct at the right border of the sternum. This murmur was conducted towards the apex. At the same time the pulse became collapsing in character. There were many crepitations at the lung bases; the liver was distended and ascites was present; and there was pitting œdema of the legs up to the knees. The urine contained a cloud of albumin and the blood urea was 98 mg. per 100 c.c. The electrocardiogram showed auricular fibrillation, normal axis deviation, and inversion of the T waves in leads I and II. The patient was too ill for cardioscopy to be undertaken. A clinical diagnosis of high blood pressure and heart failure was made, and the aortic diastolic murmur was considered to be the result of relative aortic incompetence. The response to digitalis and mercurial diuretics was poor and the patient died after three weeks in hospital, having developed pyrexia and terminal broncho-pneumonia.

Post-mortem examination (Dr. W. W. Woods). There was great œdema of legs, thighs, and back. In the skin of the upper part of the back, between the shoulders, and the lower part of the back of the neck, there were many confluent dilated veins, more numerous on the right side than on the left. The heart, which weighed 624 g. (22 ounces), showed moderate hypertrophy without dilatation of the left ventricle, slight dilatation of the left auricle, considerable hypertrophy and dilatation of the right ventricle which formed the apex of the heart, and even greater dilatation of the right auricle, particularly of its appendage. In the right auricle, at the junction of the anterior and septal cusps of the tricuspid valve, there was an orifice (0.7 cm. in diameter). The opening was fimbriated and the irregular fringe projected about 1 cm. above the surface of the valve (Fig. 1). A probe, passed through this opening, appeared at the bottom of the anterior sinus of Valsalva: the opening here was on

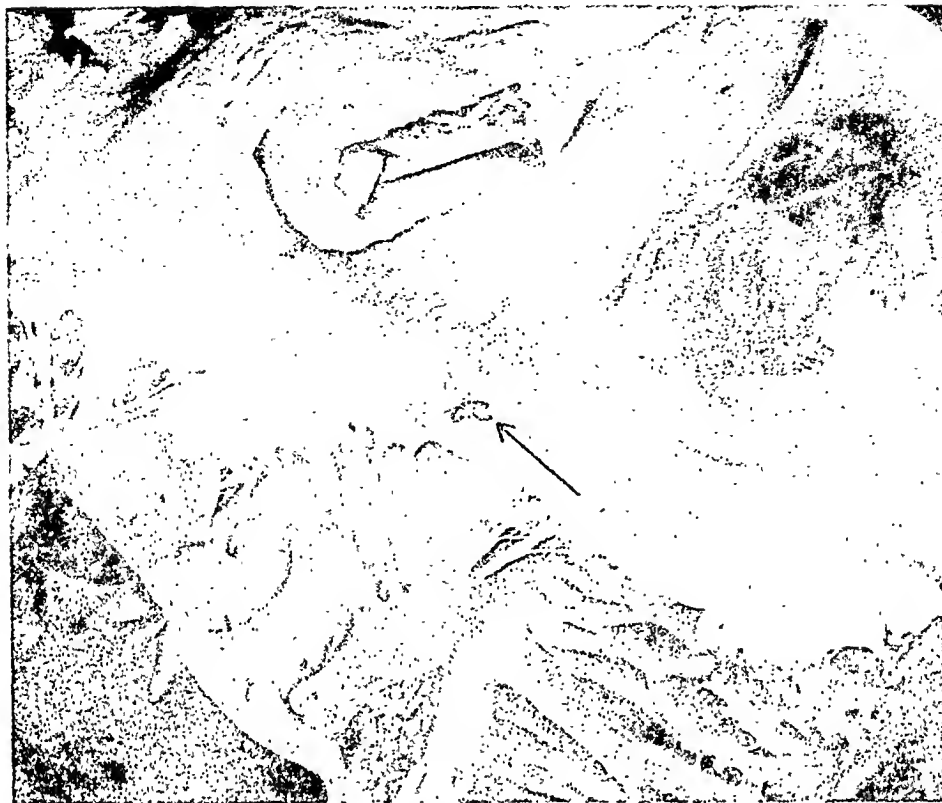


FIG. 1.—Interior of the right auricle. The opening of the cardio-aortic fistula is seen with a fimbriated and irregular fringe projecting about 1 cm. above the surface of the valve. The fimbriated opening (indicated by an arrow) is at the junction of the anterior and septal cusps of the tricuspid valve.



FIG. 2.—The aorta and aortic valves, showing the cardio-aortic fistula (indicated by an arrow) at the bottom of the anterior sinus of Valsalva.

the left side of the sinus and was 1 cm. in diameter (Fig. 2). The communication between the aorta and auricle was lined by smooth endocardium; there were no vegetations or thickenings. There were no other congenital abnormalities. The aortic valve was competent and measured 8.2 cm. in circumference. The pulmonary valve measured 10.5 cm. in circumference. All valve cusps were normal. Apart from one small button in the anterior descending branch, the coronary arteries were free from atheroma. There was moderate atheroma of the aorta. The pulmonary artery and its branches in the lungs were dilated and there were numerous fat flecks in the larger branches. The lungs showed œdema and congestion, and bronchopneumonic consolidation involved the upper half of the left lower lobe. The right thorax contained 70 c.c. (2.5 oz.) of clear fluid and the left contained 42 c.c. (1.5 oz.). The abdomen contained 370 c.c. (13 oz.) of clear fluid. The liver was enlarged and showed areas of slight central congestion. The spleen was slightly œdematous and congested. The kidneys were firm from back-pressure congestion; there was no marked fibrosis, but the arcuate arteries were slightly thickened. The changes at necropsy were consistent with hypertensive heart failure and the effects of the cardio-aortic fistula.

DISCUSSION

Localized defects of the aortic septum may lead to abnormal communication between the base of the aorta and the pulmonary artery or the pulmonary conus. When the opening is from the aorta to the right ventricle or right auricle it usually results from the rupture of a congenital aneurysm of one of the sinuses of Valsalva. Such an aneurysm arising from the posterior sinus of Valsalva and projecting into the right auricle and rupturing there a few hours before death was described by Goehring (1920). He reviewed five similar cases that had been reported; in only one case did an aneurysm from the anterior sinus lead into the right auricle. Abbott (1919) described a case in which an aneurysm of the right sinus of Valsalva had ruptured into the pulmonary conus. A correct clinical diagnosis was made in this case in which a continuous roaring murmur was heard; its accompanying vibration was so marked that it shook the bedclothes. In Goehring's case a loud rough diastolic murmur was heard in the third intercostal space to the left of the sternum and there was a systolic murmur also. Sudden collapse of the patient six hours before death was presumed to correspond with the rupture of the aneurysm. Brown (1939) mentions two cases of sudden death in young people resulting from rupture of an aneurysm of the sinus of Valsalva, into the right auricle and ventricle in one case and into the pericardial cavity in the other.

In the case reported here it is probable that the fimbriated opening was the outcome of a ruptured congenital aneurysm, but there was no episode in the patient's history that would indicate when the rupture took place. The fistula satisfactorily explained the presence of the diastolic murmur and the prominent venous congestion. The case is of further interest because of the age the patient had attained without incurring the most serious and common complication of such congenital lesions—bacterial endocarditis.

SUMMARY

An unusual case is recorded of an elderly man who showed at necropsy a cardio-aortic fistula, which led from the bottom of the anterior sinus of Valsalva to the right auricle near the tricuspid valve.

This communication illustrates a rare cause of a diastolic murmur heard along the right border of the sternum.

I would like to thank Dr. Horace Evans for permission to publish this case, Dr. William Evans for his help and advice, and Mr. John King for the photographs.

REFERENCES

- Abbott, M. E. (1919). *Contributions to Medical and Biological Research, New York*, 2, 899.
Brown, J. W. (1939). *Congenital Heart Disease*, London.
Goehring, C. (1920). *J. Med. Research*, 42, 49.

MERCURIAL DIURETICS

THE ADDITION OF MAGNESIUM SULPHATE TO PREVENT THE TOXIC EFFECTS OF THEIR INTRAVENOUS ADMINISTRATION

BY

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The importance of mercurial diuretics in the treatment of heart failure has been obvious ever since the discovery of these useful drugs. Subsequent studies have explained to some extent the mechanism of their action. The relief afforded to the heart by the administration of mercurial diuretics in cardiac failure depends on the elimination of œdema, on the decrease of the volume of circulating blood, and sometimes on the fall of the arterial blood pressure. The interaction of these factors throws much less burden upon the exhausted heart. The disappearance of œdema is itself of great importance. This is accompanied, as has been shown by Blalock *et al.*¹, by the decrease of the volume of blood flow needed by the tissues for their metabolic requirements, and a reduction of the mechanical resistance of the tissues to the flow of blood. The fall of blood pressure noted many times by various observers after the improvement of the circulation, which can perhaps be attributed to the diminution of local venous pressure in the kidney (Corrigan and Pines²), acts also in the same direction.

To these must sometimes be added an increase in the functional capacity of the heart muscle because of a decrease in the heart œdema itself, as well as the complicated effects of the relief of congestion of other important organs. So, for instance, the diuresis after mercurial diuretics has a very favourable influence upon cardiac dyspnœa and on the congestion of the lungs. Also the abdominal circulation is much improved because there is less engorgement of the liver. Finally, the disappearance of the discomfort to which the patient with heart failure is exposed, the recession of insomnia and of the cough, the improved absorption of certain nutritional factors and in particular of vitamins, the decrease of basal metabolism, all these and other factors make the improvement due to diuresis induced by mercurial diuretics even more striking.

It is not surprising, therefore, that mercurial diuretics are highly rated amongst other drugs used in heart failure. According to Thomson,³ Marvin,⁴ and others their diuretic effects are often as great with digitalis as without it. Fishberg⁵ points out that they not only "supplement the digitalis, but instances are not rare in which mercurials are decidedly more efficacious than digitalis" itself. Withering's discovery is considered generally to be the opening of the first chapter in the efficient treatment of heart failure. There cannot be the slightest doubt, then, that the introduction of mercurial diuretics by Saxl and Heilig⁶ has marked the beginning of the second period.

The diuretic properties of mercurials were known, of course, even before the papers of Viennese authors appeared. According to Goodman and Gilman,⁷ calomel was used by Paracelsus for this purpose in the sixteenth century. Later on, Jendrassik,⁸ in 1886, confirmed the beneficial action of this drug upon patients suffering from cardiac dropsy. Fourneau and

Mellville⁹ quote the important investigations of Blumenthal and Oppenheim¹⁰ in which several organic and inorganic mercury compounds were studied and demonstrated, perhaps with the exception of mercury chloride, to possess various grades of diuretic activities. Nevertheless, the true interest of clinicians was aroused only by the introduction of mercury salicylate by Saxl and Heilig⁶ and only since then the mercurial diuretics have been commonly used in the clinic for the treatment of cardiac dropsy and other diseases accompanied by the accumulation of important amounts of fluid in the tissues. This was due perhaps to the fact that, as was proved by the last mentioned authors, mercury salicylate or merbafen and even the less toxic salyrgan or mersalyl, produce much more pronounced diuresis than other mercury compounds, as for instance, mercury chloride or mercury succinate.

Since the beginning of the era of the mercurial diuretics, however, it has been known that they are not without certain toxic influence. Saxl¹¹ was clearly opposed to the administration of these diuretics in cases of severe anæmia, cachexia, fever, or diarrhœa, and advised great prudence in dealing with patients whose blood pressure was above 200 mm. The most pronounced toxic effects were, of course, registered at the sites of the excretion of mercury from the body, i.e. the kidney and colon. The essence of the diuretic action itself consists chiefly, as was demonstrated, of the irritation of the renal tubules by the mercurial ion and "represents a very early stage of the toxic action of mercury on the kidney" (Goodman and Gilman⁷). The administration of mercurial diuretics is accompanied sometimes, therefore, by the appearance in the urine of hyaline and granular casts, albumin, leucocytes, and erythrocytes, and by more or less marked degeneration of the epithelium of the tubules. The effects on the digestive apparatus, on the other hand, are also those of typical mercury poisoning and appear in the form of stomatitis, salivation, and hæmorrhagic colitis. These changes, if present before the administration of mercurial diuretics, were automatic contra-indications against their use. Nevertheless, with greater experience acquired in dealing with these drugs, the initial precautions taken in their administration were to some extent relaxed. Amongst kidney diseases, cases of nephrosis or amyloidosis react sometimes beautifully to mercurial diuretics and no physician will hesitate to use them to free the patient from the great discomfort and danger of anasarca. The signs which were originally considered as strong contra-indications, as for instance, albuminuria, heightened blood pressure, presence of increased amount of casts and red blood cells in the urine, increase of non-protein nitrogen in blood, are known to accompany sometimes the stasis kidney and do not exclude *a priori* the use of these valuable drugs. The only important contra-indications that remain from the renal point of view are an inflammatory disease of the kidney, i.e. an acute or chronic glomerulonephritis, and malignant nephrosclerosis (Scherf and Boyd¹²), and the only sign which deserves much attention and suggests prudence is the presence of diminished specific gravity of urine as a possible manifestation of renal insufficiency. Moreover, in recent times it has been proved that in most cases even of chronic nephritis there was no "evidence that the kidneys have been injured by the mercury" (Marvin⁴), and some authors (Petersen,¹³ Tursz,¹⁴ and Pines¹⁵) used successfully mercurial diuretics in the treatment of desperate anuria cases. In these latter instances the action of mercurial diuretics can be perhaps compared to the water treatment of Volhard¹⁶ of some anuric or severely oliguric patients with acute glomerulonephritis in which the drinking of 1500 c.c. of water within one-half hour can force the existent renal block (Fishberg¹⁷).

Concerning the digestive tract the only true contra-indication is the presence of ulcerative colitis (Marvin⁴). The really severe colitis with diarrhœa and bloody stools as the consequence of the administration of new mercurial diuretics is extremely rare and does not take place if the renal function is not impaired. A slightly increased number of stools following the injection, on the other hand, though perhaps a warning signal, is not by itself a contra-indication to the further use of the drugs. And stomatitis and excessive salivation according to Stokes¹⁸ and De Graff and Nadler¹⁹ are not always very reliable signs of mercurial intoxication and depend to the same extent "on the bacterial flora of the mouth and incidental conditions as on the dose of mercury that the patient is receiving.

Unfortunately, together with this recent evidence proving that the use of mercurial diuretics might be entirely safe in cases that previously were considered as not fit to receive even a small quantity of these drugs, new toxic reactions have been described, some of them connected with the drug itself and some with the diuresis that follows its administration. Moreover, some of these toxic reactions can be foreseen and eventually avoided or treated successfully; some of them, however, are unforeseeable and can lead to death in a most rapid and unexpected way.

Many of the alarming or even fatal reactions occur relatively late after the injection of the mercurial diuretic. This by itself indicates the existence of a stronger connection with the diuretic effect than with the mercurial diuretic itself. Fishberg¹⁷ describes three fatal circulatory collapses developed between 8 and 14 hours after the intravenous injection of salyrgan to patients with coronary thrombosis. He attributes the fatal result to the sudden mobilization of a large amount of fluid into the blood stream with the exhaustion of the overburdened heart. Such an explanation is obviously open to certain doubts. The diuresis after the injection of mercurial diuretics starts relatively soon, about 2 to 3 hours after administration and ceases 9 to 21 hours afterwards. Taking into consideration the late occurrence of the fatal reaction and its peripheral character, it is more plausible to assume that the considerable dehydration and diminution of the circulating blood volume was the trigger mechanism of the collapse. Many authors mention dehydration and hæmoconcentration, together with a negative chloride balance as a result of the administration of mercurial diuretic in spite of the persistence of œdema (Degraff and Nadler¹⁸). Some years ago Fourneau and Mellville⁹ attributed, in an experimental study, the chronic intoxication following the use of mercurial diuretics to "some derangement in the animal's water metabolism rather than to associated nephritis." Degraff and Nadler¹⁸ point out that the deficiency of salt interferes with the excretion of water and can provoke the mercurial poisoning due to the incomplete elimination of the drug. The same authors quote Hines²⁰ as well as Evans and Paxon²¹ as representing the opinion that azotæmia appears rather as a consequence of the rapid elimination of great quantities of œdema fluid than of the damage suffered by the kidneys from the mercury. Symptoms of chloride depletion are generally seen after the copious diuresis following mercurial diuretics. Sometimes these are relatively mild and the patients complain of weakness and of pains, particularly in the calf muscles. Other times a severe picture of great chloride depletion, comparable to heat prostration or pernicious vomiting with apathy, somnolence, severe mental symptoms, and eventually death, can develop.

Another type of alarming or fatal reaction following mercurial diuresis can be related to digitalis toxicity. Since 1931 there have appeared various studies indicating that the œdema fluid of digitalized patients can contain large quantities of this drug and produce even toxic reactions when the œdema fluid finds its way rapidly into the blood stream during mercurial diuresis. Biological methods were used in these studies and the authors have proved on hearts of frogs and cats that the œdema fluid of digitalized patients is rich in digitalis or digitalis-like substance. Degraff and Nadler¹⁸ point out that their experience is in accord with these studies and that symptoms of digitalis intoxication appear even when the patients had not received digitalis for several days. Personally we have seen many cases in which toxic symptoms have developed, which could be attributed to redigitalization depending on mercurial diuresis, and agree with them that some precautions must be taken before giving mercurial diuretics to fully digitalized patients. It is, however, worth while to stress that some authors consider that the evidence with respect to the redigitalization which occurs when the œdema fluid enters quickly into the blood stream is not complete and that toxic symptoms can depend as well on many other factors, as for instance, the loss of large quantities of sodium base which gives rise to prostration or a shift of the acid-base equilibrium towards the alkalosis with all its symptoms, such as nausea and vomiting.

Finally a copious diuresis leads sometimes to the fall in serum sodium or calcium. A fall in serum calcium was noted by some observers and others have reported spontaneous tetany development after mercurial diuresis, though this latter was not always accompanied by the diminution of calcium in serum. Degraff and Nadler also mention that grand mal attacks have been attributed in epileptics sometimes to mercurial diuresis.

The careful analysis of other toxic symptoms or signs that appear after mercurial diuretics proves that some of them depend rather on the drug itself than on the diuresis, and that the causal mechanism of others is relatively uncertain. To this latter group belongs perhaps the delayed reaction as described by Wexler and Ellis²² in the form of typical asthma attacks or pulmonary œdema. Especially the pulmonary œdema can be thought to depend on a great quantity of fluid entering rapidly into the blood stream and creating an unsupportable burden for the exhausted heart. Both their cases, which developed pulmonary œdema 120 and 80 minutes respectively after the intravenous injection

of 2 c.c. of mercurpurin, were in the state of cardiac failure, and this seems to speak in favour of such a comment. On the other hand, the pulmonary œdema can be attributed to the toxic effect of mercury upon the heart muscle, and the bronchial asthma to a manifestation of an allergic reaction or of an idiosyncrasy.

Hypersensitive reactions are also well-known from other observations and appear in various forms. About two years ago Fox, Gold, and Leon ²³ described a case in which the injection of mercurpurin and the administration of mercurin by rectal suppository, although the first 60 injections were well tolerated, led invariably to a severe reaction with fever, rash, nausea and vomiting, thoracic constriction, paresthesias, and swelling of the lips. The reaction developed invariably even when the dose of mercurpurin was very small and contained only 4 mg. of mercury, although the second phase of this reaction consisted of signs characteristic of mercury poisoning, i.e. ulcerative stomatitis. The authors conclude rightly that the reaction was not dependent on the liberation of an ionized mercury, because there was no hypersensitiveness to other organic or inorganic mercury compounds, whose administration produced marked diuresis with only a negligible reaction or without any reaction at all.

In the same year Higgins ²⁴ described a similar case in which the hypersensitive reaction manifested itself one hour after an intravenous or intramuscular injection of mercurpurin under the form of a severe chill, fever, dyspnoea, cyanosis, rapid fall in blood pressure and prostration, all of these symptoms and signs developing in rapid succession. The author points out he excluded the possibility of any cardiorespiratory lesion by the absence of any electrocardiographic evidence and by rapid disappearance of all these disturbances. According to him the fact that the reaction did not appear after three previous injections and that it bore some similarity to the reactions encountered after the administration of arsenicals supports the view that the reaction was of an anaphylactic type. He quotes some reported fatalities that occurred after intravenous injections of mercurial diuretics and not seeing any material difference between his experience and the reactions reported, suggests a new investigation of the toxicity of mercurial diuretics. He did not take into consideration apparently that the reactions described in other cases appeared only after the intravenous injection of the drug, that they manifested themselves much sooner after the injection had been effected, and that all available clinical evidence pointed to a cardiac character of such reactions described by other authors. Degraff and Nadler ¹⁹ collected other hypersensitive reactions and mention among others, cutaneous eruptions in the form of urticaria, small reddish spots or purpuric areas, morbilliform and scarlatiniform erythema, chills, fever, and even reactions resembling a state of shock with sweating, cyanosis, collapse, and urinary suppression. They quote in this respect the investigations of Wilson ²⁵ who demonstrated by patch tests that these reactions may be of an allergic character and the observation of Parent ²⁶ that the individual susceptibility plays in the development of these reactions an important rôle.

All these reactions analysed above have been known for a long time, and have been connected with mercurial diuretics by all authors. Many times they could be foreseen or even avoided, and generally they appeared in lesser or greater degree independently of the route of administration. Moreover, the mechanism of these reactions is in many cases well known as was previously said. Also, the rôle of the kidneys in this respect has been thoroughly considered, and the contra-indications to the use of mercurial diuretics in some renal diseases precisely established. The same is true of the metabolism of salts and water, and it is well known that both of these factors must be carefully watched when mercurial or other diuretics are being given. With reference to redigitalization, there was always a certain difference of opinion, but in the main the diuretic mercurial is injected before the full digitalization of the patient is reached, or the quantities of mercurial are small, around 0.5 c.c., in order to avoid a violent reaction. Although hypersensitive reactions cannot be foreseen, even in these cases certain precautions can be taken by diminishing the initial dose of the drug, or by changing one preparation for another, or finally by adding certain substances like calcium gluconate to the mercurial diuretic before injection. Altogether, the known mechanism of reactions, the thorough analysis of contra-indications, and the precautions used in the injection of mercurial diuretics have brought about a relatively great degree of safety for the patients in the use of these drugs, and even when the reactions developed sometimes after the injection, they were of minor significance, and only extremely rarely alarming or fatal. There is, however, another type of toxic reactions appearing after mercurial diuretics that are completely different from all other reactions considered above, and the mechanism of which has only lately begun to be better understood and known.

The main features of this new type of reactions are as follows: (1) They manifest themselves in the clinic only after the intravenous route of administration, though there are certain suspicions in respect also to peritoneal route. (2) They appear very soon after the injection is over, generally from a few seconds to 5 or at most 10 minutes, and stop within a very short time if they are not fatal. (3) There is experimental and clinical evidence that these reactions happen because of disturbances in the specific heart musculature and perhaps also in the active musculature of the ventricles. (4) The peripheral vascular collapse was not observed during these reactions and, therefore, they are probably not of an anaphylactic nature (Wexler and Ellis²²). (5) The reactions are often severe and in great proportion they lead to immediate death. (6) Relatively small quantity of the drug or its high dilution does not always prevent the appearance of disturbances (Degraff and Nadler¹⁹). (7) It seems that the reactions are more severe in the presence of considerable heart failure, though many of them have been described without heart insufficiency at all (cases of nephrosis). (8) They appear sometimes after the first injection, but sometimes also after the patient has received as much as 164 c.c. of mercupurin (Wexler and Ellis²²); sometimes all previous injections produce rather benign symptoms as in both fatal cases of Wexler and Ellis, or the previous injections are supported without any untoward symptoms as happened in Wilson's²⁵ cases. (9) Sometimes all measures taken including epinephrine injections cannot prevent death (for instance, Carrillo's⁴⁵ case), but sometimes epinephrine injections or other measures like morphine and oxygen seemed to be helpful (fourth case of non-fatal immediate reaction of Wexler and Ellis). (10) The reactions appear with particular frequency after esidrone and mercupurin injection, though sometimes the exchange of mercupurin for salyrgan does not prevent the reaction (first case of Barker, Lindberg, and Thomas²⁷).

This new type of toxic reaction after the intravenous administration of mercurial diuretics and in particular after mercupurin or esidrone seems so dangerous to everybody who has seen it (the senior author's 2 cases) that some authors are already demanding a re-examination of the whole subject of mercurial diuretics (Higgins²⁴ and Friedfeld, Kissin, Modell and Sussman²⁸), some recommend great prudence in intravenous administration (Carrillo⁴⁵), and some recall that the diuretic response after intramuscular injection is often sufficiently abundant and that after intramuscular injection no fatalities as yet have been reported, or directly recommend the intramuscular route.

It is true that, as Wexler and Ellis²² point out, the frequency of severe or fatal reactions after the intravenous administration of mercurial diuretics is relatively low. In the reports available to us we find 26 cases analysed by Degraff and Nadler¹⁹ in 1942 beginning from Redlich's²⁹ cases reported in 1926, i.e. for a period covering 16 years. To these must be now added 2 cases of Levin³⁰ quoted by Carrillo,⁴⁵ his own case, 2 cases seen by the senior of the authors, and 2 fatal and 5 alarming (immediate) non-fatal reactions encountered by Wexler and Ellis during 16 months in the Boston City Hospital. Though, perhaps, the statement of Degraff and Nadler in respect of the lowness of toxicity of mercurial diuretics as compared with the toxicity of arsphenamines still holds good, we do not believe that in the case of mercurial diuretics the state of the literature actually reflects the real toxicity of these drugs. This depends in part on the fact that the fulminant reactions have been known and understood only a relatively short time, in part because until ten or twelve years ago, the less toxic salyrgan and neptal were used instead of the more toxic novurit, esidrone, and mercupurin, in part because in the early years of mercurial diuretics intramuscular injections were used much more frequently than intravenous injections, in part because not all fatal reactions were attributed to the mercurial diuretics as the patients were in a very bad shape at the moment of injection, and finally in part because of unknown reasons.

The use of intravenous injections of mercurial diuretics in the treatment of heart disease is raising problems of increasing importance. Many authors (Fishberg,⁵ Levine³²) stress the efficiency of intravenous injections even when the intramuscular route does not give a

good diuresis, but already some hesitate very much before choosing this route. For example, Goodman and Corsaro³³ refer to the toxicity of mercurial diuretics by intravenous injections, saying that only the intramuscular route was used in their study. Such an attitude is even more justified by the results of experimental studies.

After the initial experiments of Dresser³¹ in 1893, Mueller, Schoeller, and Schrauth³⁴ described in 1911 an acute type of intoxication with mercury compounds which led to an immediate death in cats. In 1922 Salant and Kleitman³⁵ performed their perfusion experiments with inorganic and organic mercury salts on a turtle heart and showed that a mercury compound independently of its anion produces disturbances of heart action particularly of the cardiac rhythm. The time at which these appeared depended on the concentration of the mercury salt, though when the experiment was carried on for long enough "delirium cordis" developed with dilutions as high as 1/10,000,000. They showed, too, that in dogs, "delirium cordis" resulted from the intravenous injections of inorganic mercurial salts and mercurochrome; and Salant and Kleitman's results with cats and dogs were similar to those obtained in more recent studies on the toxicity of organic mercury compounds. In 1923 Hatcher and Weiss³⁶ attributed the emesis appearing after the intravenous injections of mercury chloride to direct reflexes from the heart. In 1926 Jackson³⁷ studying the pharmacologic action of organic mercury compounds on the heart reported that 5 c.c. of a 2 per cent solution of salyrgan (about 100 mg. of salyrgan and 39.6 mg. of mercury) were producing regularly within 3 to 5 minutes the death of normal dogs through ventricular fibrillation. In 1929 McCrea and Meek³⁸ proved that larger doses of mercury compounds produce pathological rhythms of the animal heart. In 1931 Fourneau and Mellville⁹ confirmed the results of Mueller, Schoeller, and Schrauth³⁴ in respect of the "hyperacute fulminant" type of intoxication immediately after the intravenous administration of mercury compounds, but though "no definite lesions could be found in the central nervous system," they attributed the intoxication to the action on the central respiratory mechanism. In the same year Salant and Nagler³⁹ when studying the effect of calcium and potassium on cardiac reactions to mercury, and making use of the isolated frog heart with Straub's method, found that mercury (bichloride) in concentrations above 1/500,000 in normal Ringer acted upon the conduction system as well as upon the active musculature of the heart producing the decrease of force and frequency of contractions and a certain irregularity of cardiac action; the cardiac resistance to mercury was considerably diminished in the hypodynamic heart, and also by interrupted treatment with mercury. After giving a solution 1/100,000 within about 30 minutes in certain experiments there was a progressive depression of the heart, whereas in others, the heart action was becoming weaker and irregular, extrasystoles and heart block manifesting themselves and persisting for a long time. The auricle was much more resistant against mercury than the ventricle, and calcium protected the heart from the toxicity of mercury compounds partially perhaps by decreasing permeability of cellular membrane, while potassium and mercury often showed synergism in their action upon the heart muscle.

The results of those older investigations have been fully confirmed by more recent studies. Chastain and Mackie⁴⁰ in 1940 administering large intravenous doses of esidrone to normal dogs under barbiturate anaesthesia observed within 12 to 15 seconds after the injection deviation of the T waves, followed by ventricular flutter, fibrillation, and death. One year later Johnston⁴¹ showed similar results of intoxication with mercury salts, but added that the isolated turtle heart as well as the heart of the intact cat could recover if subjected to after-treatment with sodium thiosulphate. In 1942 Barker, Lindberg, and Thomas²⁷ in an extensive study gave various mercurial diuretics intravenously to 30 normal dogs with and without intravenous barbitol anaesthesia. Death was produced always by a particular pattern composed of depression of T waves, ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation. The results were exactly the same in the anaesthetized animals as in 4 vagotomized animals, in 2 animals with the cervical cord and both vagi severed, and in instances of an isolated perfused heart. From Fig. 1, 2, and 3 of their paper it is seen that the authors used in those experiments 2 c.c. of salyrgan, 2.2 c.c. of salyrgan and theophylline, and 1.4 c.c. of mercupurin. Otherwise the equivalent amounts of organic or inorganic mercury compounds were administered. The authors feel that "the mercury ion acts directly on the ventricular muscle to produce ventricular fibrillation and death."

In the same year another excellent study was presented by Degraff and Lehman,⁴² in which many pertinent data with reference to the acute toxicity of mercurial diuretics were firmly established. In experiments on cats and using the scheme similar to the proposed U.S.P.XII cat assay for digitalis the authors found the mean lethal dose for every mercurial diuretic frequently used by the medical profession. This mean lethal dose is the smallest for esidrone and greatest for salyrgan-theophylline, esidrone without theophylline, salyrgan, mercurin, and mercupurin occupying intermediary places

between those two extremes. Moreover, they proved that the previous administration of digitaline Nativelle, aminophylline, ammonium chloride, and soluble phenobarbital had no influence upon the mean lethal dose, and that even a slow rate of intravenous injection of mercurial diuretic to man did not give a guarantee against a lethal reaction. Some suggestions in respect to the slight protective action of a great dilution of the drug were also made, but one animal out of three died at a dilution of the drug as high as 1/25. Finally the conclusion was drawn that the lethal reaction is due exclusively to the cardiac action of the drug, the terminal event being ventricular fibrillation or respiratory failure depending on circulatory failure, and that the more gradual intravenous administration or the intramuscular injection of considerable quantities of mercurial diuretic produce successively the T wave changes accompanied by the fall of arterial and venous pressures, rapid ventricular tachycardia, and in case the heart does not recover, death through ventricular fibrillation or complete respiratory failure because of fall of arterial blood pressure. The authors also point to some experimental evidence that epinephrine can improve the heart poisoned by mercury, whereas ergotamine rather increases the toxicity of these drugs, and that the favourable influence of sodium thiosulphate and sodium formaldehyde sulphonylate upon the heart disturbances provoked by the injection of mercurials must be further investigated.

In addition to these investigations Wexler and Ellis²² state that there is strong clinical evidence that in man the mechanism of lethal superacute or fulminant reaction to the intravenous injection of mercurial diuretics is exactly the same as in case of animals, and that "at present there is no known way of preventing fatal reactions."

In conclusion, the mercuric ion liberated from organic mercurials produces abundant diuresis through its action upon the renal tubules, but simultaneously in certain doses, and if appearing rapidly in the blood stream of a mammal, it provokes serious disturbances in the conduction system of the heart as well as in the musculature of the ventricles. Previous research has established in general lines the mechanism of this phenomenon, but certain details are still lacking, and even more important no pertinent method has been indicated in order to avoid fatal or alarming reactions in man, especially when we are dealing with serious lesions of heart muscle. It seems of great urgency and importance, therefore, to find out if certain changes introduced in the chemical composition of mercurial diuretics or certain substances added or incorporated into them could prevent fatal reactions in human beings, and thus re-establish the safety of intravenous injections. If certain substances must be added to mercurial diuretics, to prevent fatal reactions they should, according to us, possess three other following qualities: viz., they should not diminish the diuretic qualities of mercurials but should if possible increase them by a synergistic action; they must be innocuous in the doses recommended; and finally, they must mix well with mercurial diuretics without forming a precipitate.

The search for such a substance or substances together with the effort to increase our knowledge in respect of the mechanism of fatal reactions was the principal purpose of the present study.

METHOD

Dogs were used for the present experiments. In all cases we applied general anæsthesia through the intravenous injection of pertinent amounts of somnifen Roche, because as was proved by Barker, Lindberg, and Thomas,²⁷ the phenobarbital anæsthesia does not change the character of reaction due to injection of mercurial diuretics. Moreover, as the respiratory failure is only a secondary phenomenon and follows disturbances in heart action, artificial respiration was used in nearly all experiments. In a few, in which we did not open the chest of the animal and did not need, therefore, artificial respiration, the results were just the same as in all others. After the trachea was opened and artificial respiration applied, we proceeded in most experiments to open the chest in the usual way, trying to avoid all unnecessary hæmorrhage. The pericardial sac was opened by a broad triangular dissection and its borders fixed to the chest walls. The disturbances of heart action were observed directly

and registered by means of electrocardiogram taken sometimes in the first, sometimes in the second lead, and sometimes in both. The Cambridge string electrocardiograph was used throughout.

The experiments consisted in partially intravenous and partially intracardiac injections of different amounts of esidrone. The injections were given sometimes into the cavity of the right auricle, sometimes into the cavity of the left ventricle or auricle, and sometimes into the jugular vein which was dissected beforehand and left free for this purpose. We were unable to observe any marked difference in the influence of esidrone upon the heart depending on the different place of injection. In the beginning by intracardiac or intravenous injection of 4 c.c. of esidrone we provoked the appearance of ventricular tachycardia followed within a few seconds by ventricular fibrillation. Later on, we convinced ourselves that the above-mentioned disturbances followed by a complete standstill of heart ventricles could be provoked in a dog of between 6 and 14 kg. of weight by an injection of only 2 c.c. of esidrone, though the ventricular fibrillation and complete heart standstill appeared a little later than by using 4 c.c. Nevertheless, the difference of time was only of seconds or of minutes, because even when 2 c.c. of esidrone were injected, the ventricular fibrillation appeared at most within 2 to 3 minutes after injection. At the end of the first phase of our experiments we injected intracardially or intravenously different amounts of 20 per cent solution of sulphate of quinine. This last drug not only did not hinder the appearance of ventricular fibrillation but it can be said that in all three experiments in which the sulphate of quinine was injected almost at once after the esidrone injection, ventricular fibrillation manifested itself at once, i.e. even earlier than was expected from previous experiments with esidrone. Later on we proceeded to inject magnesium sulphate after the full content of esidrone ampoule, i.e. 3 c.c. had been used. This method was changed for the simultaneous injection of magnesium sulphate with esidrone. In the beginning of the magnesium sulphate part of our study 2 c.c. of a 20 per cent solution together with 2.3 c.c. of esidrone were used tentatively. The dose of magnesium sulphate seemed too high, however, because, though the appearance of ventricular fibrillation was much delayed or did not produce itself, the cardiographic changes in respect of the disturbances of auriculo-ventricular and intraventricular conduction were even more marked than in the case of esidrone injection only. We observed also that when enough magnesium sulphate (10 c.c. of 20 per cent solution) was injected even after the esidrone was used, the heart would stop suddenly because of the complete cessation of its automatic function but without having passed through the phase of ventricular fibrillation. On the base of such and similar observations and reasonings the proper dose and timing of the magnesium sulphate injections were arrived at. In the last part of our experiments we were injecting the full amount of esidrone ampoule together with 0.5 c.c. of a 20 per cent solution of magnesium sulphate. The injections were effected with half-hour intervals between one another and no persisting heart disturbances were noted. Using this last method as many as seven times the lethal dose as established in previous experiments could be injected intravenously or intracardially and the heart still returned to the sinus though a little slower rhythm with disappearance of auriculo-ventricular and intraventricular block.

RESULTS

As already stated, we were able to confirm the experience of previous authors in respect of the unfavourable effect of certain doses of mercurial diuretics introduced rapidly into the blood stream upon the conduction system and the active musculature of the ventricles.

No effects upon the respiratory centre could be observed, however, because we were using artificial respiration, as we believe together with Degraff and Lehman⁴² that the changes in the respiratory centre during the course of fulminant intoxication with mercurial diuretics are completely secondary and depend in the first place on the fall of arterial blood pressure.

The doses administered to dogs chosen on the base of the mean lethal dose established for normal cats by Degraff and Lehman have proved themselves a little too high because those quantities of esidrone injected intracardially or even intravenously provoked ventricular fibrillation almost at once and did not permit observation of the course of intoxication. So, for instance, in one experiment the intracardiac injection of 4 c.c. of esidrone to a dog of 17 kg. produced immediately intraventricular block and a few seconds later irreversible ventricular fibrillation, although the lethal dose for this dog as calculated on the base of mean lethal dose established for cats by Degraff and Lehman would be 4.08 c.c. of esidrone (Fig. 1). In other experiments when we administered esidrone by the jugular vein similar

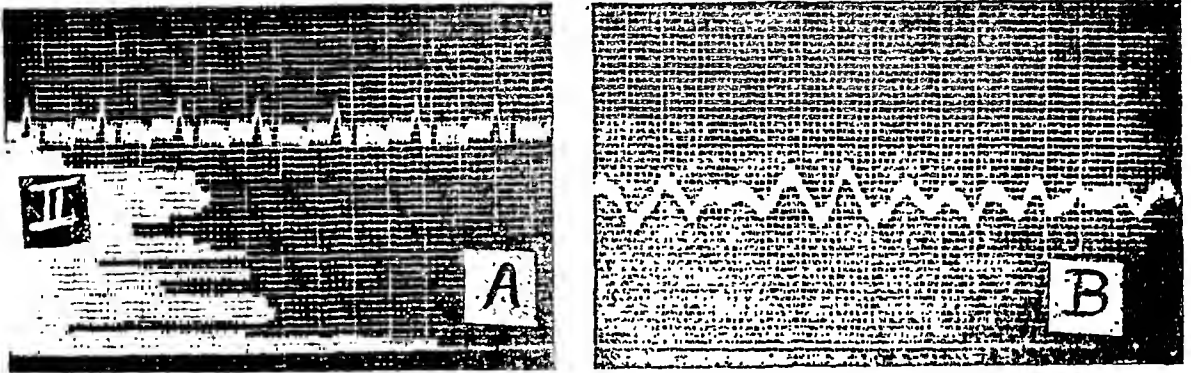


FIG. 1.—(A) Before injection of esidrone: normal rhythm; frequency 136 a minute; P-R, 0.12 sec.; QRS, 0.04 sec.; T negative, 1.5 mm. (B) Instantaneous ventricular fibrillation after injection of 4 c.c. of esidrone.

results were obtained. At the end of our first stage of experiments, therefore, we diminished considerably the dose of esidrone and injected dogs of even above 10 kg. with a quantity of esidrone which varied between 1 and 2 c.c. This was always enough to provoke the fulminant intoxication with ventricular fibrillation appearing within 2 to 5 minutes, thus enabling us to observe better all electrocardiographic changes. This agrees with Barker, Lindberg, and Thomas,²⁷ who obtained ventricular fibrillation and death by injecting a dog of 7 kg. with a dose of mercurin not higher than 1.4 c.c., although according to Degraff and Lehman's data for cats the lethal dose for this dog should have been 5.8 c.c. We have no other explanation for this fact than the possible influence of barbital anæsthesia used by us as well as by Barker, Lindberg, and Thomas in spite of the fact that these authors did not find proofs for the existence of such a difference, and also perhaps the fact that we were administering the full lethal dose at once, together with the difference between two species.

From this first part of our experiments two other facts are also apparent. The anoxia of heart muscle increases its sensitivity to intoxication by mercurial diuretics, as in two experiments in which the artificial respiration apparatus ceased to work because of some defect of its mechanism, ventricular fibrillation appeared at once, and thus much earlier than we could expect on the base of our previous experience with the same dose of esidrone. This perhaps can explain to some extent why a failing heart and in particular infarcted heart muscle seems to be more sensitive to mercurial intoxication (Fishberg¹⁷).

Another fact which we observed concerns the development of intoxication. Degraff and Lehman,⁴² as well as Barker, Lindberg, and Thomas,²⁷ describe a particular pattern of mercurial intoxication consisting of early changes of the T wave, followed by disturbances in intraventricular conduction, ventricular extrasystoles, ventricular tachycardia, ventricular flutter and fibrillation, and death. In some of our experiments, however, we were able to observe a more uniform action of mercurial diuretics upon the heart conduction system, as on a parallel line with T wave changes and intraventricular conduction defect, there appeared some disturbance of auriculo-ventricular conduction (Fig. 2). This agrees with the clinical

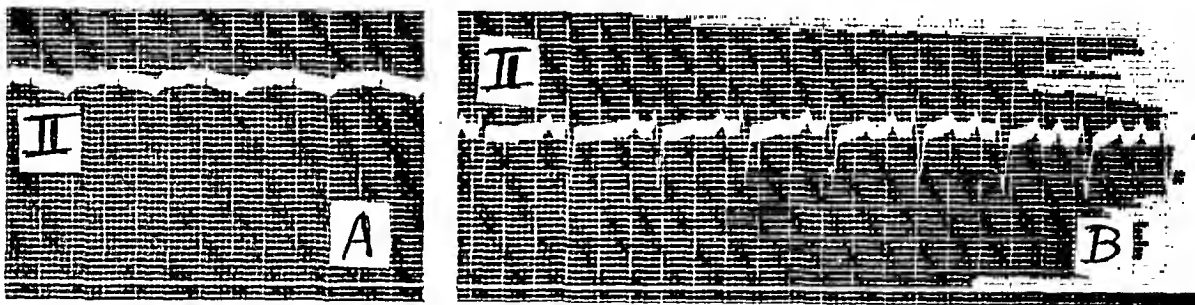


FIG. 2.—(A) Before injection of esidrone: normal rhythm; frequency 111 a minute; P-R, 0.12 sec.; QRS of small amplitude and 0.03 sec.; T negative, 2 mm. (B) After injection of 2.3 c.c. of esidrone: normal rhythm; frequency 115 a minute; P-R, 0.18 sec.; QRS broad, deformed, with S wave deep in form of staircase ("en marche d'escalier"), and 0.16 sec.; T positive, 3mm. Simultaneous appearance of auriculo-ventricular and intraventricular conduction disturbances after esidrone.

observation of Wexler and Ellis,²² who in one case of rheumatic heart disease with auricular fibrillation mention the appearance of periods of complete heart block with a ventricular rate around 50 during acute intoxication with mercurial diuretics.

Finally, from the first part of our study it seems that sulphate of quinine not only has no hindering effect upon the development of ventricular fibrillation in the course of intoxication with mercurial diuretics, but on the contrary rather accelerates it, as is well seen from Fig. 3A, B, and C, where the administration of 0.25 g. of sulphate of quinine has, if anything,

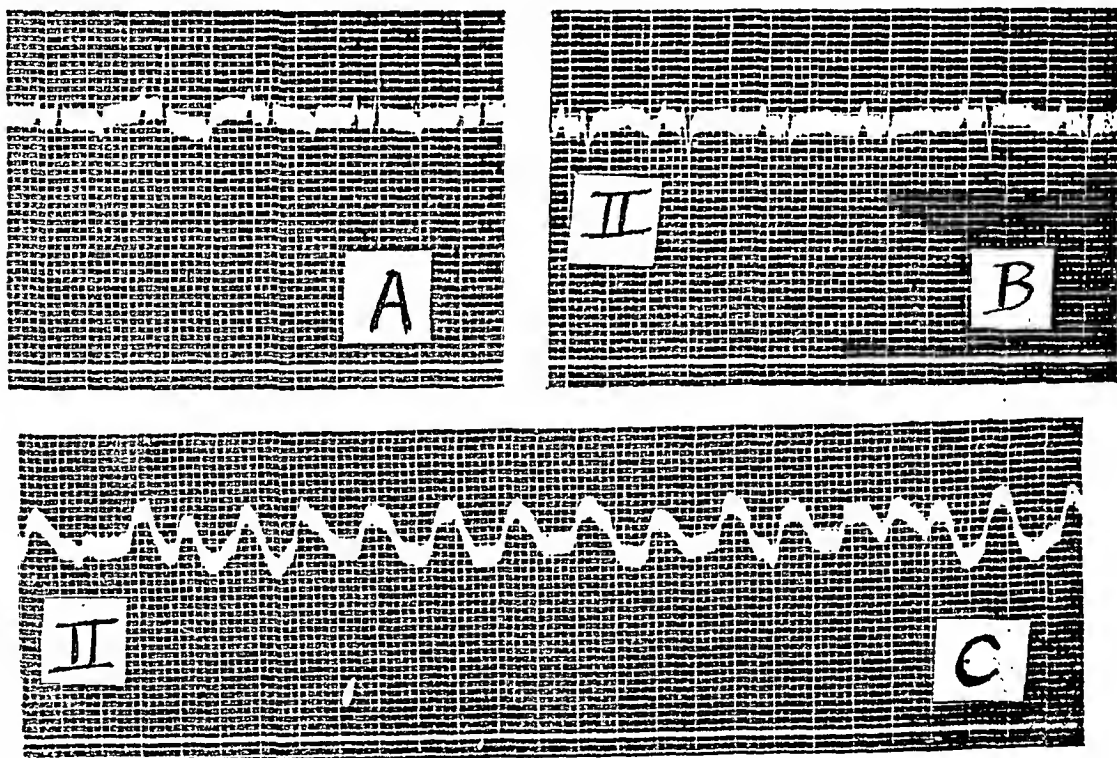


FIG. 3.—(A) Before injection of esidrone: normal rhythm; frequency 120 a minute; P-R, 0.11 sec.; QRS, 0.04 sec.; T negative, 1.5 mm. (B) After injection of 1 c.c. of esidrone: normal rhythm; frequency 120 a minute; P-R, 0.12 sec.; QRS completely changed, of small amplitude, and 0.08 sec.; T positive, 0.5 mm. (C) Instantaneous ventricular fibrillation after injection of 1 c.c. of a 25 per cent solution of quinine.

quickened the mercurial reaction. This effect of quinine and quinidine especially in greater amounts is well known from experience with even healthy heart muscle (Boyd and Scherf,⁴³ Goodman and Gilman?).

From the second part of our experiments the conclusion must be drawn that magnesium

sulphate has a suppressing effect upon the ventricular fibrillation provoked by the administration of mercurial diuretics. This tendency is well seen from one experiment, in which 10 c.c. of a 20 per cent solution administered within 2 minutes after the injection of 2.3 c.c. of esidrone and in a moment when disturbances of intraventricular conduction had already manifested themselves, hindered the appearance of ventricular fibrillation, though the action of the heart ceased suddenly after the short period of considerable disturbances in auriculo-ventricular and intraventricular conduction. The possibility of a kind of synergistic action of magnesium sulphate and of mercurial diuretic in toxic doses upon the conduction system of the heart induced us to diminish greatly the dose of magnesium sulphate and in order to assure a favourable effect, we began to inject this last substance simultaneously with esidrone. In these latter experiments we observed a very favourable action of 0.5 c.c. of a 20 per cent solution of magnesium sulphate upon the course of heart intoxication due to intracardiac or intravenous injection of esidrone. Thanks to this suppressive action of magnesium sulphate in the dose mentioned, we could administer up to seven times the dose which we have every reason to consider as lethal, without any persisting ill effects upon the heart action. This does not mean that 0.5 c.c. of a 20 per cent solution of magnesium sulphate always and totally arrested the reaction due to the administration of a mercurial diuretic in the dose known as lethal. Sometimes the disturbances of the conduction system did not manifest themselves at all after the first dose of 2.3 c.c. of esidrone. Sometimes they did, however, and always appeared after the second 2.3 c.c. dose of esidrone. But they never continued and the heart of the animal after a certain time, generally less than 30 minutes, returned to sinus rhythm, though often slower than before, the ventricular complexes acquiring normal aspect and the T waves returning nearly to their previous shape.

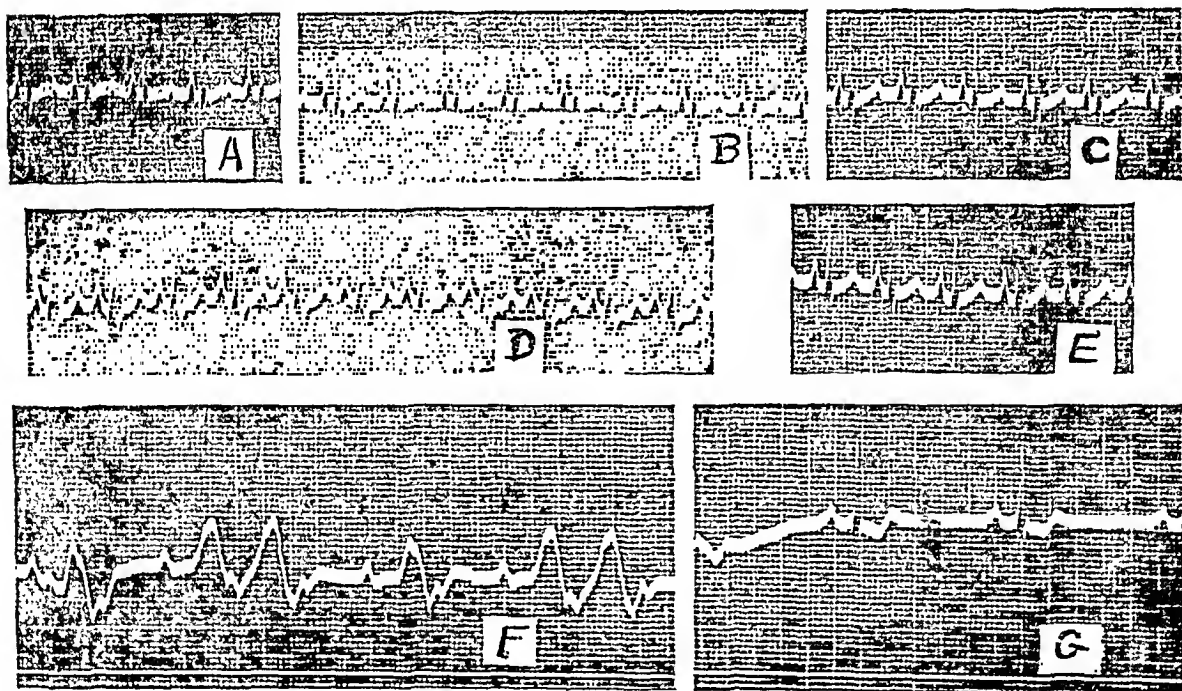


FIG. 4.—Repeated injection of esidrone. All lead I. (A) Before injection of esidrone: sinus rhythm; frequency 143 a minute; P-R, 0.10 sec.; QRS, 0.05 sec.; T positive, 1 mm. (B) Normal appearance after injection of 2.3 c.c. of esidrone and 0.5 c.c. of a 20 per cent solution of magnesium sulphate. (C) The same within 5 minutes after the second injection of the same combination of drugs. (D) After third injection of esidrone and magnesium sulphate: sinus rhythm; frequency 143 a minute; P-R, 0.12 sec.; QRS, 0.12 sec.; T positive, 2 mm. (E) Electrocardiogram returning to its normal aspect within 5 minutes after third injection of esidrone and magnesium sulphate. (F) After sixth injection of 2.3 c.c. of esidrone and 0.5 c.c. of a 20 per cent solution of magnesium sulphate. Complete heart block and atypical ventricular complexes. Auricular frequency 130 a minute. (G) After seventh injection of esidrone and magnesium sulphate: sinus rhythm; frequency 49 a minute; P-R, 0.24 sec.; QRS, 0.08 sec.; T diphasic.

To illustrate better this influence of magnesium sulphate we should like to describe with more detail the course of one of these last typical experiments. The weight of the dog was 12 kg. After a deep anaesthesia, induced through the intravenous injection of 10 c.c. of somnifen, we proceeded to artificial respiration and chest opening in the above described way. The pericardial sac was opened and fixed to the chest borders. The cardiogram is normal in all respects, the heart frequency being 142 a minute (Fig. 4A).

The first injection of 2.3 c.c. of esidrone +0.5 c.c. of a 20 per cent solution of magnesium sulphate did not produce any appreciable changes during half an hour of observation. The second injection of the same combination of drugs, on the contrary, produced the appearance of intraventricular, though not very intensive, conduction defect. Moreover, these intraventricular conduction disturbances lasted for only a very short time, ceasing completely after about 5 minutes, when Fig. 4C was taken. The third injection produced more intraventricular conduction defects accompanied by prolongation of P-R, but even this time the cardiogram returned within 5 minutes to its normal (Fig. 4E). The following fourth, fifth, and sixth injections produced even more accentuated changes in the intraventricular and auriculo-ventricular conduction including complete auriculo-ventricular block and a few times an atypical ventricular complex, but invariably after perhaps a little more time, although well below half an hour, sinus rhythm was re-establishing itself (Fig. 4G). At the end, after 5 hours, the experiment was interrupted without the appearance of ventricular fibrillation.

All experiments done in the same way gave similar results, although sometimes we could induce ventricular fibrillation by repeating at small intervals of time the injections of a dose as high as 4 c.c. of esidrone. The conclusion was drawn, therefore, that magnesium sulphate has a hindering effect upon the ventricular fibrillation due to intoxication of mercurial diuretics, though it does not suppress the ill effects of the injections of excessive doses and generally does not hinder the appearance of some disturbances in the auriculo-ventricular or intraventricular conduction.

COMMENT

From clinical observation and from experiments upon animals, confirmed also by this study, we can now reconstruct the influence of the mercurial compounds upon the heart muscle. In certain doses they are powerful depressants for the whole of the heart muscle. This action is much weaker upon the higher segments of the heart but increases rapidly beginning from the A-V node. In this respect we can confirm Salant and Nagler,³⁹ who have proved that the auricle was much more resistant to mercurial compounds than the ventricle, and the recent observations of Barker, Lindberg, and Thomas,²⁷ that after the ventricular electrical impulses have stopped, the auricles continued to beat in a regular sinus rhythm. We had the opportunity to observe the same phenomenon many times. This does not mean, however, that the mercurial compounds have no influence upon the S-A node or upon the auricular muscle. Simultaneously with the appearance of complete heart block nearly always a small decrease of the auricular rate, and therefore, a slight decrease of the frequency of impulse formation in the S-A node, could be noted. After recovery from mercurial intoxication a slower sinus rhythm is the rule according to the investigations of ourselves and other authors (Degraff and Lehman⁴²). This recalls to some extent the direct influence of quinidine upon the S-A node.

The depressive influence of mercurial compounds upon the A-V node is, however, much stronger, as in the case of quinidine or quinine. It was recorded by us many times in the form of latent, partial, or complete heart block and was confirmed by Wexler and Ellis's²² clinical observation of periods of complete heart block during the recovery from mercurial toxic reaction in a case with auricular fibrillation. Moreover, this depressive action of mercurials upon A-V conduction explains also the mechanism of the appearance of the bundle branch block. According to Pines⁴⁴ it can be always questioned whether the asynchronism of contraction of the ventricles is caused by the acceleration of conduction in one bundle branch or its slowing in the other, unless there is strong evidence that we are dealing with a phenomenon or a drug which has a depressing action upon various segments of the conduction system. In the case of mercurials such evidence seems to be furnished by their influence upon A-V conduction.

It is more difficult to explain the mechanism of changes in the T waves recorded by all authors who have studied the mechanism of hyperacute intoxication provoked by mercurial compounds. There was a relatively old report of Jackson³⁷ that salyrgan acts on the heart through the stimulation of the vagi and that as soon as the vagus control is removed, death ensues, not because of heart failure but because of paralysis of the respiratory centre. On the other hand, as we know from the studies of Samojloff⁴⁰ and Rothberger and Winterberg⁴⁷ that the vagus stimulation produces T waves of small amplitude, the T wave changes occurring in the early stage of mercurial intoxication might depend on the stimulation of the vagus nerve. This explanation is, however, not very probable. Jackson³⁷ did his experiments on dogs under ether anaesthesia. Kobacker and Rigler,⁴⁸ on the other hand, found on cats in 1929 that ether anaesthesia paralyzes the vagus nerve. The same was known from Ruttger's⁴⁹ experiments on the heart of the frog. Moreover, Steinfeldt⁵⁰ proved that the pulse frequency increases during ether anaesthesia, and Rothberger⁵¹ observed that the respiratory arrhythmia due to the central excitation of vagus and so well marked in the morphinized dog, disappears immediately after the beginning of the ether anaesthesia. Finally, Pines,⁵² in 1934, demonstrated that this effect depends not so much on the diminution of the effect of acetylcholine, but rather on the partial or complete arrest of the secretion of vagus substance. On the basis, therefore, of these experiments the results obtained by Jackson³⁷ are open to certain doubts. And still more so because Salant and Kleitman,³⁵ as well as Barker, Lindberg, and Thomas,²⁷ demonstrated directly by means of bilateral vagotomy or atropinization that the suppression of the influence of the vagus nerve does not change the action of mercurials upon the heart. The changes of the T waves recorded during the early stages of intoxication with mercurials must be, therefore, attributed rather to the toxic effect upon the active musculature of the heart which is known from the experiments of Salant and Nagler,³⁹ among others, particularly that the increase of strain on either or both ventricles does not enter into consideration before the mobilization of the peripheral fluid has time to occur.

Concerning the ventricular fibrillation reported and observed by all authors as well as by us as the final result of an acute mercurial intoxication, very little need be added. It is well known that many myocardial depressants and myocardial stimulants alike can produce ventricular fibrillation. Even quinidine itself, which has certain value in preventing and alleviating ventricular fibrillation, when administered in excessive doses results in ventricular fibrillation in experimental animals (Katz⁵³). Mercurial compounds probably act in a similar way. As a matter of fact we have found a certain synergism between the influence on the heart of large doses of quinine and of mercurial compounds in the later stages of acute mercurial intoxication.

The action of magnesium sulphate in preventing the lethal effects of acute intoxication with mercurial diuretics, must, on the other hand, be considered separately as it is of considerable importance, practically and theoretically.

Magnesium is apparently indispensable for life of the mammals and plants (Goodman and Gilman⁷). Its concentration in human serum is according to current opinion between 2 and 3 mg. per 100 c.c., and in red corpuscles about 4 mg. It is interesting to note its high concentration in cardiac muscle and its fall in cases of cardiac failure. According to Harrison⁵⁴ the left ventricle of the normal cardiac muscle contains about 20 mg. of magnesium, whereas the same ventricle of patients who died from congestive heart failure contained only 16 mg. of magnesium per 100 g. of fresh tissue. Pharmacologic properties of magnesium salts have been studied for a long time. Smith, Winkler, and Hoff⁵⁵ mention in their paper that the results of their investigations in respect of the action of magnesium on the mammalian heart are in agreement with older experiments of Hay⁵⁶ effected in 1882 and relatively more recent investigations performed by Matthews and Jackson⁵⁷ in 1907. With reference to the influence of magnesium sulphate on the mammalian organism there was particularly fruitful research connected with the efforts of Meltzer and Auer⁵⁸ and of other authors in order to introduce this drug for general and local anaesthesia. It has been found that parenteral administration of magnesium sulphate induces general anaesthesia (Meltzer and Auer); that there is a certain synergism between the action of magnesium salt and ether or morphine

(Gwathmey⁶⁰ and others); that the solution of magnesium sulphate paralyses the exposed motor and sensory nerves (Meltzer and Auer,⁶⁸ Liljestrand,⁶⁰ and Guthrie and Ryan⁶¹); that the chief danger of parenteral administration of magnesium sulphate consists primarily in the paralysis of respiration due in cases of moderate doses mainly to the curare action, and that only much greater quantities can produce cardiac arrest due to well known cardio-inhibitory action of magnesium; that magnesium sulphate can be useful in the symptomatic treatment of tetanus (Kocher⁶²; Meltzer⁶³) and against strychnine and other convulsants; that after the magnesium sulphate anaesthesia there can appear some diuresis together with cylindruria and glycosuria. Later on the magnesium sulphate was recommended for the treatment of asthmatic crises and of endarteriitis obliterans as well as for certain diagnostic and therapeutic procedures like estimation of circulation time or duodenal drainage (Meltzer and Lyon⁶⁴ test).

According to Boyd and Scherf⁴³ the first effort to use the cardio-inhibitory properties of magnesium for the treatment of heart disturbances is due to Seekles,⁶⁵ who administered magnesium chloride intravenously to eliminate arrhythmias depending on the injection of calcium chloride into cows suffering from milk fever or grass staggers. But the real interest in these properties of magnesium was only evoked when Zwillinger⁶⁶ recommended in 1935 the intravenous injections of 10 c.c. of a 20 per cent solution of magnesium sulphate for the treatment of paroxysmal tachycardia and ventricular premature beats or ventricular flutter. One year later Rothberger and Zwillinger,⁶⁷ in very extensive animal experiments succeeded in preventing or eliminating the ventricular tachycardias caused by barium or by digitalis previously known as irreversible. Rothberger⁶⁸ pointed out with insistence that the property of arresting the otherwise irreversible digitalis or strophanthine ventricular tachycardias is unique and characteristic for magnesium sulphate, the inhibitory action of which is much more strong upon the ectopic pacemakers than upon the S-A node.

The cardio-inhibitory action of magnesium salts was also studied not long ago by Smith, Winkler, and Hoff.⁵⁵ They proved that its chief action on the heart consists in the general depression of conduction, i.e. depression of sino-auricular, auriculo-ventricular, and intra-ventricular conduction, the action upon this latter being, however, not so extreme as to provoke the disorganization of the whole ventricular complex, as in case of potassium. The recommendation of Zwillinger to use magnesium salts in order to prevent ventricular flutter and extrasystoles, on the other hand, has been found to be based on scant physiological evidence because such arrhythmias could be induced or appeared spontaneously in the presence of greatly increased concentration of magnesium in the serum.

The clinical evidence, however, presented in the recent paper of Boyd and Scherf⁴³ confirms entirely the experience of Zwillinger and of Rothberger and Zwillinger, and seems to indicate the usefulness of intravenous administration of a 20 per cent solution of magnesium sulphate in cases of paroxysmal auricular and ventricular tachycardia.

The results of our study also confirm the views of Zwillinger, Rothberger and Zwillinger, and Boyd and Scherf. We have convinced ourselves that the addition of small quantities (0.5 c.c.) of a 20 per cent solution of magnesium sulphate to the intravenous or intracardiac injection of a lethal dose of mercurial diuretic prevents ventricular fibrillation and death of the animal, although particularly after the second and following injections it does not prevent the development of some disturbances of conduction. This is especially marked when the magnesium sulphate in this small dose is given simultaneously with mercurial diuretic. In this way one is able to inject with relatively small intervals of time (about half an hour) doses as much as 7 to 8 times higher than the dose known as lethal for normal dogs, and no persisting harmful effects are apparent. Even when magnesium sulphate is given after the injection of the mercurial diuretic in a lethal dose, it has analogous effect, because it arrests the heart without the phase of ventricular fibrillation, as we had the opportunity to observe a few times.

There seems to be no direct contradiction between the results of our study and those obtained by Smith, Winkler, and Hoff.⁵⁵ Many other drugs which in certain conditions are capable of preventing or alleviating ventricular fibrillation, in excessive doses can produce

ventricular fibrillation in experimental animals (Katz⁵³). This refers to quinidine, potassium salts, and even to stimulation by faradic current. Boyd and Scherf⁴³ also mention this paradoxical double influence of cardio-inhibitory drugs and by it explain the frequent appearance of ventricular extrasystoles after the intravenous injection of magnesium sulphate. It is clear, therefore, why magnesium sulphate did not suppress ventricular fibrillation in Smith, Winkler, and Hoff's experiments when the magnesium content of the serum reached an extraordinarily high level of 36 mg. per 100 c.c., although the inhibitory function of this drug upon the stimulus formation can in other conditions, whether clinical or experimental, be so obvious.

The mechanism of this protective action of magnesium sulphate upon the development of ventricular fibrillation in the course of acute intoxication provoked by the intravenous or intracardiac injection of organic mercurial diuretic is not known. A faint suggestion in respect of this mechanism can be looked for, however, in the fact that the injection of magnesium with the mercurial diuretic is more efficient than when it follows the injection of the mercurial diuretic at even only relatively very small interval of time. Some years ago Salant and Nagler³⁹ attributed the decreased toxicity of mercurial ion for the isolated heart produced by great doses of calcium, to the diminished permeability of the cell membrane. An analogous action of magnesium is known from the study of the nervous system and was brought to the fore by Moore⁶⁹ to explain its analgesic rôle. Possibly, therefore, this property of magnesium together with its inhibitory action are responsible for the protective influence offered by it in cases of acute intoxication by mercurial diuretics. Independently, however, of the exact details of this mechanism magnesium sulphate in pertinent doses and injected simultaneously with the mercurial diuretics, seems according to our study to correspond with our first postulate as mentioned in the introduction of this paper, i.e. to exert a protective action on the heart in the course of an acute intoxication by mercurial diuretics).

On the other hand, magnesium does not only not suppress the diuretic activity of mercurial diuretics, but rather increases the diuretic effect of organic mercurial compounds. A certain diuretic property of this drug was known already to Meltzer and Auer,⁵⁸ who noted that after anaesthesia with magnesium sulphate there is some diuresis but not diarrhoea. White,⁷⁰ in the new edition of his book, lists also magnesium sulphate among diuretics with no very strong diuretic properties when given alone. It is possible that this diuretic action is due mainly to the presence of the sulphate anion in magnesium sulphate molecule, which anion being rejected by the renal tubule is a powerful osmotic diuretic (Goodman and Gilman⁷). Particularly clear is the diuretic activity of magnesium sulphate when administered together with mercurial diuretics. The senior of the authors many years ago used to inject intramuscularly a mixture of organic mercurial compound with 2 to 3 c.c. of a 20 per cent solution of magnesium sulphate, and observed beautiful diuretic responses. The theoretical reason for use of such a mixture was the Elias'⁷¹ hypothesis that diuretic mercurials are initially excreted in bile, and only when re-absorbed from the digestive tract produce their diuretic action. All drugs, therefore, capable of increasing the secretion of bile as, for instance, decholin or perhaps also magnesium sulphate had to be considered according to this hypothesis as provided with synergistic properties in respect of the mercurial diuretics. An analogous mixture, but with much greater content of magnesium sulphate and with the addition of 1.5 c.c. of a 5 per cent procaine hydrochloride, was used for intramuscular injections by Shelling and Tarr,⁷² and Marvin⁴ expresses the belief that there can be no question "that this combination is sometimes remarkably efficacious with patients who have shown little or no response to salyrgan." Thus magnesium sulphate fulfils the second of our postulates to the effect that injected simultaneously it increases diuretic properties of mercurial diuretics.

Finally, the intravenous injection of such small quantities of magnesium sulphate (0.5 c.c. of a 20 per cent solution) together with mercurial diuretic seems to be completely safe. Boyd and Scherf⁴³ employed in their series the injection of a 20 per cent solution in amounts from 10 to 20 c.c., even for cases with coronary sclerosis or myocarditis, and no "untoward effects have been observed." They quote the observations of other authors according to which magnesium salts have been given in concentration from 10 to 30 per cent to patients with coronary sclerosis, angina pectoris, etc., without any alarming reaction. Magnesium sulphate in a concentration as high as 42 per cent, though with the addition of calcium gluconate, has been also used many times for the estimation of circulation time, apparently without ill effects. The same refers to dogs, because Moore and Wingo⁷⁴ injected their dogs with large doses of

magnesium chloride, and when the injection was stopped before the occurrence of the respiratory arrest some animals survived without permanent injuries although the blood Mg level reached 20 to 24 mg. per 100 c.c. Schmidt and Greenberg⁷³ estimate the fatal dose of $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ for a dog with normal serum calcium as between 0.23 and 0.28 per kg. We have injected our dogs of a weight of around 10 kg. with 0.5 c.c. of a 20 per cent solution or 0.1 g. of magnesium sulphate, or 0.01 g. per kg. The therapeutic index (relation between fatal and effective dose) was therefore on the base of these data 25 : 1.

The assumption is justified, therefore, that the doses of magnesium sulphate employed by us are completely safe for dogs and particularly for man, and that magnesium sulphate fulfils the third of our postulates, i.e. it is absolutely safe in the doses recommended. We believe that incorporation of small quantities of magnesium sulphate into the solution of mercurial diuretics should be made in order to prevent fatal reactions resulting from intravenous injection of these drugs: in addition, magnesium sulphate mixes with mercurial diuretics without forming any precipitate.

SUMMARY

The course of acute intoxication produced by the intravenous or intracardiac injections of esidrone was studied on normal dogs with the help of the electrocardiograph. It is concluded in agreement with other authors that mercurial diuretics in certain doses are general depressants for the whole cardiac muscle. The following pattern of intoxication was observed: changes of T waves, intraventricular and auriculo-ventricular conduction disturbances, diminution of frequency of impulse formation in S-A node, ventricular paroxysmal tachycardia, chaotic heart action, ventricular fibrillation, and death.

The addition of small quantities of magnesium sulphate (0.5 c.c. of a 20 per cent solution) prevents ventricular fibrillation and death, even if doses 7 times higher than normal lethal doses are used. Magnesium sulphate, however, does not prevent and even perhaps increases the conduction disturbances resulting from the administration of lethal doses of mercurial diuretics. On the other hand, such amounts of magnesium sulphate increase the diuretic response, are entirely safe, and mix with mercurial diuretics without forming any precipitate.

It is suggested that small quantities of magnesium sulphate be incorporated into the mercurial diuretics in order to prevent fatal reactions resulting sometimes from the intravenous injections of these drugs.

REFERENCES

Owing to the arrangement of this paper, it has been thought best to make an exception to the usual custom and to leave the references in the form presented by the Author, except that the year where given is put after the author's name.—EDITOR.

1. Blalock, A., Pilcher, C., and Harrison, T. R. (1929). *Amer. J. Physiol.*, **89**, 589.
2. Corrigan, F. P., and Pines, I. (1943). *Surgery*, **14**, 88.
3. Thomson, W. A. R. (1937). *Quart. J. Med.*, **6**, 321.
4. Marvin, H. M. (1940). *J. Amer. med. Ass.*, **114**, 757.
5. Fishberg, A. M. (1937). *Heart Failure*. H. Kimpton, London.
6. Saxl and Heilig: quoted by Fishberg (17).
7. Goodman, L., and Gilman, A. (1941). *The Pharmacological Basis of Therapeutics*. Macmillan & Co., New York.
8. Jendrassik: quoted by Fishberg (17).
9. Fourneau, E., and Mellville, K. I. (1931). *J. Pharmacol. exper. Therap.*, **41**, 21.
10. Blumenthal, F., and Oppenheim, K.: quoted by Fourneau and Mellville (9).
11. Saxl: quoted by Fishberg (17).
12. Scherf, D., and Boyd, L. J. (1939). *Cardiovascular Diseases*. C. V. Mosby, St. Louis.
13. Petersen, A.: quoted by Degraff and Nadler (19).
14. Tursz: Personal communication.
15. Pines: Unpublished observations.
16. Volhard: quoted by Fishberg (17).
17. Fishberg, A. M. (1939). *Hypertension and Nephritis*. Fourth ed. Lea & Febiger, Philadelphia.
18. Stokes: quoted by Degraff and Nadler (19).
19. Degraff, A. C., and Nadler, J. E. (1942). *J. Amer. med. Ass.*, **119**, 1006.

20. Hines: quoted by Degraff and Nadler (19).
21. Evans and Paxon: quoted by Degraff and Nadler (19).
22. Wexler, J., and Ellis, L. B. (1944). *Amer. Heart J.*, 27, 86.
23. Fox, Th., Gold, H., and Leon, J. (1942). *J. Amer. med. Ass.*, 119, 1497.
24. Higgins, W. H. (1942). *Ibid.*, 119, 1182.
25. Wilson: quoted by Degraff and Nadler (19).
26. Parent: quoted by Degraff and Nadler (19).
27. Barker, M. H., Lindberg, H. A., and Thomas, M. E. (1942). *J. Amer. med. Ass.*, 119, 1001.
28. Friedfeld, L., Kissin, M., Modell, W., and Sussman, R. (1941). *Ibid.*, 117, 1806.
29. Redlich: quoted by Degraff and Nadler (19).
30. Levin: quoted by Carrillo (45).
31. Dresser: quoted by Rossello, H. J. (1940). *Terapeutica Clinica y Farmacodynamica*. Uteha, Argentina, Buenos Aires.
32. Levine, S. A. (1940). *Clinical Heart Disease*. Second ed. W. B. Saunders, Philadelphia and London.
33. Goodman, J. I., and Corsaro, J. F. (1943). *Amer. Heart J.*, 26, 338.
34. Mueller, Shoeller, and Schrauth: quoted by Fournau and Mellville (9).
35. Salant and Kleitman: quoted by Wexler and Ellis (22).
36. Hatcher and Weiss: quoted by T. Sollmann (75).
37. Jackson: quoted by Wexler and Ellis (22).
38. McCrea and Meek: quoted by Sollmann (75).
39. Salant, W., and Nagler, H. (1931). *J. Pharmacol. exper. Therap.*, 41, 407.
40. Chastain and Mackie: quoted by Barker, Lindberg, and Thomas (27).
41. Johnston: quoted by Degraff and Lehman (19).
42. Degraff, A. C., and Lehman, R. A. (1942). *J. Amer. med. Ass.*, 119, 998.
43. Boyd, L. J., and Scherf, D. (1943). *Amer. J. med. Sci.*, 206, 43.
44. Pines, I. (1938). *Wien. Arch. inn. Med.*, 32, 129.
45. Carrillo, E. G. (1943). *Rev. Med. Costa Rica*, 5, 425.
46. Samojloff, A. (1910). *Pflueger's Arch. ges. Physiol.*, 135, 417.
47. Rothberger, C. J., and Winterberg, H. (1910). *Ibid.*, 135, 506.
48. Kobacker and Rigler: quoted by I. Pines (44).
49. Ruttger: quoted by I. Pines (44).
50. Steinfeldt: quoted by I. Pines (44).
51. Rothberger: quoted by I. Pines (44).
52. Pines, I. (1934). *Arch. Internat. Pharmacodyn. Therap.*, 49, 91.
53. Katz, L. N. (1941). *Electrocardiography*. Lea & Febiger, Philadelphia.
54. Harrison, T. R. (1935). *Failure of the Circulation*. Williams & Wilkins, Baltimore.
55. Smith, P. K., Winkler, A. W., and Hoff, H. E. (1939). *Amer. J. Physiol.*, 126, 720.
56. Hay: quoted by Smith, Winkler, and Hoff (55).
57. Matthews and Jackson: quoted by Smith, Winkler, and Hoff (55).
58. Meltzer and Auer: quoted by Sollmann (75).
59. Gwathmey: quoted by Sollmann (75).
60. Liljestrand: quoted by Sollmann (75).
61. Guthrie and Ryan: quoted by Sollmann (75).
62. Kocher: quoted by Sollmann (75).
63. Meltzer: quoted by Sollmann (75).
64. Meltzer and Lyon: quoted by Sollmann (75).
65. Seekles: quoted by Boyd and Scherf (12).
66. Zwillinger (1937): quoted by Endelman and Pines. *O Czeskoskurczu napadowym czasie ciazy porodu*. Warsz. Czas. Lek.
67. Rothberger and Zwillinger: quoted by Endelman and Pines (see 66).
68. Rothberger, C. J.: Personal communication.
69. Moore, R. M. (1934-5). *Amer. J. Physiol.*, 110, 191.
70. White, P. D. (1944). *Heart Disease*. Third ed. Macmillan & Co., New York.
71. Elias: Personal communication.
72. Shelling and Tarr: quoted by Marvin (4).
73. Schmidt, C. L. A., and Greenberg, D. M. (1935). *Physiol. Rev.*, 15, 297.
74. Moore, R. M., and Wingo, W. J. (1941). *Amer. J. Physiol.*, 133, 391.
75. Sollmann, T. (1943). *A Manual of Pharmacology and its applications to Therapeutics and Toxicology*. Sixth ed. W. B. Saunders, Philadelphia and London.

CLINICAL EVALUATION OF THE PRESSOR ACTIVITY OF METHEDRINE, NEO-SYNEPHRINE, PAREDRI- NE, AND PHOLEDRINE

BY

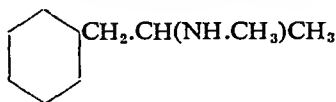
FREDERICK PRESCOTT

From the Wellcome Research Institution, London

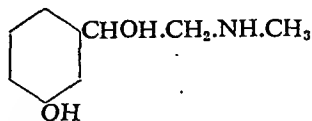
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Recently a number of pressor drugs of the adrenaline type have come into clinical use for the treatment of low blood pressure following surgical procedures, spinal anæsthesia, circulatory collapse, and surgical and traumatic shock. For therapeutic purposes the ideal pressor drug should be effective by the intramuscular or intravenous route; it should act rapidly; it should produce a sustained elevation of blood pressure, so that frequent injections of the drug are not necessary; and it should have no undesirable effects on the cardiovascular system and no untoward side effects. Adrenaline and ephedrine were the first drugs to be used clinically to raise the blood pressure in cases of operative shock. Their limitations, however, are now well known. Adrenaline may do more harm than good because in therapeutic doses intravenously it causes a considerable rise of blood pressure, e.g. 200 mm. to 300 mm. of mercury, with a precipitous fall after a few minutes to a level lower than before. Similarly ephedrine, which for dependable results must be given intravenously, produces a sharp rise of blood pressure that lasts only for ten to twenty minutes. Other pressor drugs have been introduced with a more sustained action. In most of the studies reported on these, however, no definite criteria seem to have been employed in their evaluation, nor have the conditions of administration been standardized. In general the drugs have been given to patients showing a fall of blood pressure after spinal anæsthesia or during surgical operations, but few comparative studies have been made on them.

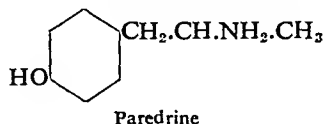
In this investigation an attempt has been made to evaluate in similar conditions the pressor activity of the sympatho-mimetic drugs methedrine (*d*-desoxyephedrine, pervitin), neo-synephrine, paredrine, and pholedrine (paredrinol, veritol). Their chemical relationship to adrenaline and ephedrine is shown in the following formulæ:



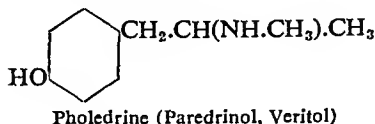
Methedrine (Desoxyephedrine, Pervitin)



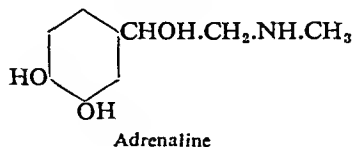
Neo-synephrine



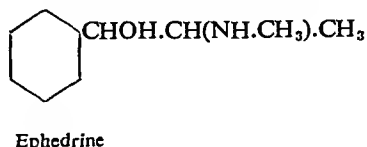
Paredrine



Pholedrine (Paredrinol, Veritol)



Adrenaline



Ephedrine

A detailed study of the pressor effects of methedrine has already appeared (Dodd and Prescott, 1943*a* and 1943*b*). The results of twenty of the cases studied are given in this paper, only those showing a severe fall in blood pressure (average 64/50 mm.) being included.

A number of studies on neo-synephrine have been published (Johnson, 1937; Lorhan and Oliverio, 1938; Bittrich, 1939; Brunner and de Takats, 1939; Silvers and Leonard, 1940; Lorhan and Lalich, 1940; Difabio, Lawrence, and Ascione, 1941) but no comparative clinical tests have been made using patients with a low blood pressure.

Several investigations have been carried out on the pressor activity of paredrine in normal subjects (Abbott and Henry, 1937; Loman, Rinkel, and Myerson, 1939; Altschule and Iglauer, 1940; Iglauer and Altschule, 1940; Myerson and Loman, 1941). Iglauer and Molle (1943) have reported on the pressor effect of paredrine on subjects suffering from infection, but most of them seemed to have a normal blood pressure and were in no need of a pressor drug. It would seem that the best way to evaluate a pressor drug is to give it to a subject with a low blood pressure and see if this can then be maintained at a normal level.

Nathanson *et al.* (1942) investigated the effect of paredrine in spinal anaesthesia. They recorded that the blood pressure was maintained during the operation in 83 per cent of 114 patients who received the drug. In the author's opinion it is not sufficient to follow the blood pressure during the operation only, say, for half to three-quarters of an hour, as the effect of some drugs does not last longer than this and a fall of blood pressure occurs when the patients are returned to the wards. In evaluating a pressor drug readings must be taken over a period of at least two hours. Altschule and Gilman (1939) also used paredrine to prevent a fall of blood pressure during spinal anaesthesia. Only one case was observed in which a satisfactory rise of blood pressure was recorded for more than two hours.

Pholedrine (veritol) has been used since 1937 on the continent to maintain blood pressure during surgical operations. It has been the subject of favourable reports by Dodd and Merton (1939), Dodd (1940, 1942), and Landau, Logue, and Kopelman (1942). In the author's series it was found that the duration of action of pholedrine was only 35 minutes and that repeated injections of the drug were necessary to maintain the blood pressure when this had fallen to 80 mm. systolic or less. In only four cases out of twenty was the response satisfactory according to the standards laid down by the author. Nathanson and Engelberg (1942) state that paredrine shows a greater and more prolonged pressor activity than pholedrine in the normal subject.

METHODS USED

The drugs were administered to patients undergoing major operations who experienced a severe fall in blood pressure. The criterion of this was a fall of systolic blood pressure to 80 mm. or less, or a pulse pressure of 10 mm. or less, that persisted for more than twenty minutes to half an hour. If the systolic or pulse pressure showed signs of spontaneous recovery in this period no pressor drug was given.

Whilst it was difficult to standardize exactly the conditions in which the drugs were given, these were much the same for all the patients. Most of the operations were done under spinal anaesthesia, or under local anaesthesia reinforced with an inhalation anaesthetic or with pentothal; a major operation, usually abdominal, was performed in all cases; and the average age was the same in all groups (about 50). The operations included those on the kidney, bladder, and ureter; cholecystectomy; gastrectomy; gastro-enterostomy; laparotomy; excision of the rectum; prostatectomy; radical mastectomy; hysterectomy; lobectomy; and repair of hernia. In most cases the drug was administered intramuscularly; in a few it was given both intramuscularly and intravenously. The intramuscular route was generally chosen because patients with a low pressure and impending shock often have collapsed veins and valuable time may be lost trying to enter them to give an intravenous injection. An efficient pressor drug should, therefore, act quickly when given intramuscularly.

No injections were given subcutaneously as it is well known that absorption from the subcutaneous tissues is slow in circulatory failure.

Each drug was given to a group of twenty patients undergoing major surgical operations, selected according to the criteria laid down above. The following were evaluated for each drug: optimum dose to produce an adequate pressor response; systolic and diastolic blood pressures before, and maximum and minimum pressures after administration of the drug; rise of systolic and pulse pressure; time for the drug to act; time taken for the systolic blood pressure to return to its pre-operative level; time taken to produce the maximum rise of blood pressure; effect on pulse rate; duration of action; the number of injections needed to sustain the blood pressure; and any untoward effects. Blood pressure and pulse readings were taken every one to two minutes until the maximum rise was recorded and then further readings were made every five minutes for the first hour and every ten minutes for the second hour. When time permitted readings were taken over a period of several hours.

Certain arbitrary standards were adopted. The time taken for the drug to act was measured by the time between the injection and a rise of 10 mm. systolic pressure. Duration of action was measured by the time the systolic pressure kept above 100 mm. The result of an injection was only rated as satisfactory if the systolic pressure kept above 100 mm. for two hours or more and the pulse pressure was not less than 30 mm. during this period. If a period longer than two hours is taken it is difficult to rule out natural recovery after this time in some of the cases, particularly if the fall in blood pressure is due to the administration of a spinal anæsthetic. It was generally found that, if the blood pressure fell during an operation as a result of spinal anæsthesia and surgical trauma, it did so within half an hour to forty minutes of the start of the operation. It is not only spinal anæsthesia that causes a fall in blood pressure but the added effect of surgical trauma (*Papper et al.*, 1943).

RESULTS

The results are summarized in Table I and presented graphically in Fig. 1. Protocols giving the results of each case and submitted with the paper have been omitted owing to lack of space. The results given in Table I are averages calculated from data obtained from the twenty cases studied with each drug. The blood pressure curves in Fig. 1 were obtained by plotting the average blood pressure of twenty cases calculated at five-minute intervals.

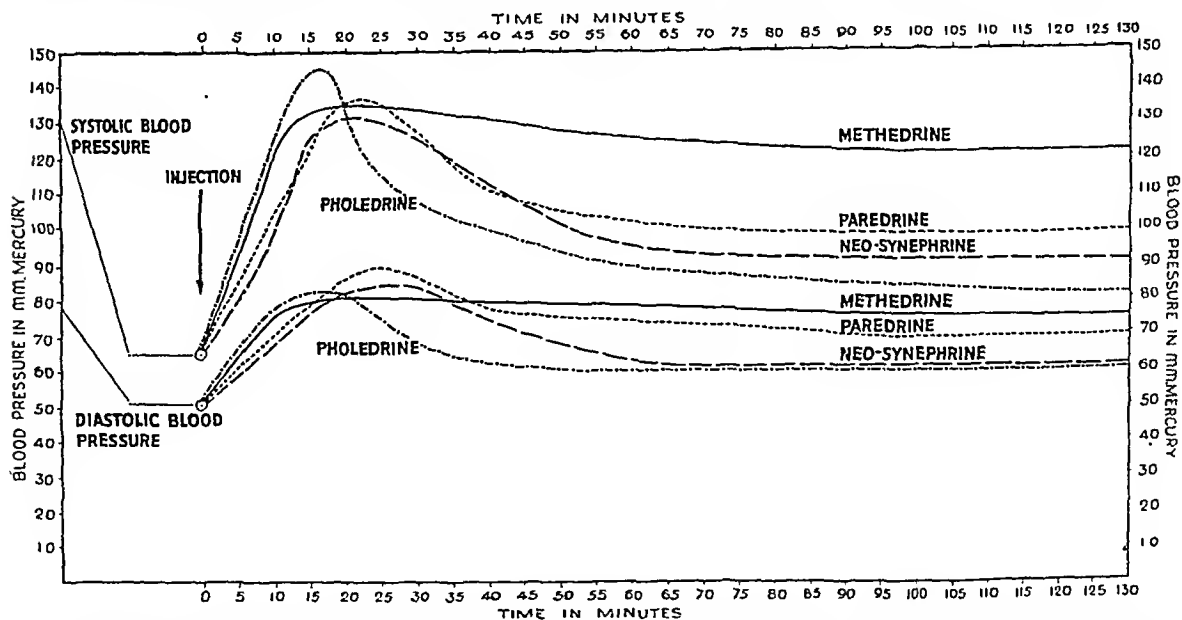


FIG. 1.—Systolic and diastolic blood pressure curves after intramuscular injection of methedrine, neo-synephrine, paredrine, and pholedrine, into surgical patients with low blood pressure. Curves are based on average values of twenty cases for each drug.

TABLE I

EFFECT OF METHEDRINE, NEO-SYNEPHRINE, PAREDRIE, AND PHOLEDRIE ON BLOOD PRESSURE AND PULSE RATE. AVERAGES OF TWENTY CASES

| Drug | Dose in mg. | B.P. before operation | B.P. just before giving drug | Max. B.P. after giving drug | Final B.P. after giving drug | Increase or decrease in pulse rate per min. | Time to act (min.) | Time to produce max. rise in B.P. (min.) | Duration of action (min.) |
|-------------------|-------------|-----------------------|------------------------------|-----------------------------|------------------------------|---|--------------------|--|---------------------------|
| Methedrine | 20-30 | 127/78 | 64/50 | 134/80 | 122/74 | +16 | 3-4 | 17 | Over 120 in 18/20 |
| Neo-synephrine .. | 5-7.5 | 125/75 | 64/50 | 132/83 | 91/62 | -11 | 8 | 23 | 42 |
| Paredrine | 10-20 | 132/81 | 67/53 | 136/90 | 99/70 | +15 | 5-6 | 25 | 60 |
| Pholedrine | 20-30 | 133/80 | 73/50 | 145/84 | 84/62 | +38 | 4 | 18 | 35 |

Dosage. The actual dose of the drug required to produce an adequate pressor response is not of great importance, unless such a dose is near the toxic level or produces unpleasant side reactions. Many pressor drugs have been evaluated in terms of the minimal dose required to produce a pressor response, the drug which produces the required response in the smallest dose being rated as the most potent. The duration of action, which is important clinically is often overlooked. In this investigation it was found that the following doses were approximately equipressor in activity when given intramuscularly:

| | |
|----------------------|------------------|
| Neo-synephrine | 5 mg. to 7.5 mg. |
| Paredrine | 10 mg. to 20 mg. |
| Methedrine | 20 mg. to 30 mg. |
| Pholedrine | 20 mg. to 30 mg. |

Repeated administration is usually necessary in the case of pholedrine and neo-synephrine to maintain a blood pressure that has fallen. Out of 20 cases repeated injections were needed in 17 patients treated with pholedrine; in 13 treated with neo-synephrine; in 12 treated with paredrine; and in 2 treated with methedrine.

Effect on Systolic Pressure. All four drugs exert an appreciable action on the systolic blood pressure (Fig. 1). The averages for the maximum systolic blood pressure, the final systolic pressure when the last reading was taken, and the final rise in systolic pressure are given below.

| | Average maximum systolic blood pressure in mm. Hg | Average final systolic blood pressure in mm. Hg | Average final rise in systolic blood pressure in mm. Hg |
|-------------------|---|---|---|
| Methedrine | 134 | 122 | 58 |
| Paredrine | 136 | 99 | 32 |
| Neo-synephrine .. | 132 | 91 | 27 |
| Pholedrine | 145 | 84 | 11 |

It is seen that whereas pholedrine produces the largest immediate rise this is not maintained, the final systolic pressure being only 84 mm. and the final rise in systolic blood pressure only 11 mm. Methedrine produced the highest final systolic pressure and the highest rise in systolic pressure. This was the difference between the systolic pressure just before the drug was injected and the final reading.

Methedrine was the only drug that kept the systolic blood pressure consistently above 100 mm.

Effect on Pulse Pressure. The pulse pressure is the difference between the systolic and diastolic blood pressures, and is a measure of the force with which blood is pumped from the

heart into the blood vessels. In shock or impending shock it is low. The normal pulse pressure is about 40 mm. In this study a pressor drug was rated satisfactory only if it maintained a systolic pressure of 100 mm. or more and a pulse pressure of at least 30 mm. The maximal and final pulse pressures and the immediate and final rise in pulse pressure are given below.

| | Average maximum pulse pressure in mm. | Average final pulse pressure in mm. | Average immediate rise in pulse pressure in mm. | Average final rise in pulse pressure in mm. |
|----------------|---|---|---|---|
| Methedrine .. | 54 | 48 | 40 | 34 |
| Neo-synephrine | 49 | 29 | 35 | 15 |
| Paredrine .. | 46 | 29 | 32 | 15 |
| Pholedrine .. | 61 | 22 | 40 | 1 |

Methedrine produced the greatest rise in pulse pressure (40 mm.) and within limits this was maintained (34 mm.). With the other drugs the pulse pressure eventually dropped to less than 30 mm. The least satisfactory drug from the point of view of permanently raising the pulse pressure was pholedrine.

Effect on Pulse Rate. Methedrine, pholedrine, and paredrine increase the heart rate; neo-synephrine slows it. The average figures and ranges are given below.

| | | | | Effect of pulse rate per minute | |
|----------------|----|----|----|---------------------------------|------------|
| | | | | Average | Range |
| Methedrine .. | .. | .. | .. | +16 | -10 to +36 |
| Neo-synephrine | .. | .. | .. | -11 | -35 to +46 |
| Paredrine .. | .. | .. | .. | +15 | -24 to +48 |
| Pholedrine .. | .. | .. | .. | +38 | -40 to +80 |

Actually the effect is variable and unpredictable. Methedrine which normally quickens the heart rate may slow it in some patients, and neo-synephrine which normally slows it, may quicken it in some.

Speed of Action. The time taken for the drug to start acting was taken as the time for a rise of 10 mm. systolic blood pressure to occur. The average time taken for the systolic blood pressure to return to its original level and the average time to produce the maximum rise in systolic blood pressure were also noted. The average times are given below.

| | | | Time to return B.P. to original level | Time to produce maximum rise in B.P. |
|----------------|----|-----|---|--|
| | | | min. | min. |
| Methedrine .. | .. | 3-4 | 13 (18/20 cases) | 17 |
| Pholedrine .. | .. | 4½ | 14 (14/20 cases) | 18 |
| Neo-synephrine | .. | 8 | 13 (14/20 cases) | 23 |
| Paredrine .. | .. | 5½ | 17 (11/20 cases) | 25 |

Methedrine and pholedrine appear to act most rapidly, then neo-synephrine, and finally paredrine.

Duration of Action. The drug with the most prolonged action was methedrine. In 18 out of 20 cases the duration of action was over two hours. Only 2 cases were recorded in which the drug failed to maintain the blood pressure above 100 mm. systolic or the pulse pressure at 30 mm. or more for two hours.

Next in order came paredrine. The average duration of action in the 20 cases was 60 minutes. In only 8 out of 20 cases, however, was the effect prolonged for two hours or more.

The duration of action of neo-synephrine averaged 42 minutes in the 20 cases. In 13 of them it averaged 30 minutes. In only 7 cases out of 20 was the effect prolonged for two hours or more.

Pholedrine was the most evanescent of the four drugs in its action. The average duration

of action was 35 minutes. In only 4 cases out of 20 was the effect of the drug prolonged for two hours.

REACTIONS FROM THE DRUGS

The commonest side effect produced by these drugs is a disturbance of cardiac rhythm and the production of systolic heart murmurs. These effects are transient and usually do not last for more than a few hours. In each patient the cardiovascular system was examined clinically before and after giving the drug. The fewest cardiac disturbances were experienced with methedrine and the most with neo-synephrine. The results are summarized below.

| | | Extrasystoles and other disturbances of rhythm | Apical and pulmonary systolic murmurs | Altered heart sounds |
|----------------|-------|--|---|-------------------------|
| Neo-synephrine | .. | 5 | 3 | 1 |
| Pholedrine | | 5 | 2 | — |
| Paredrine | | 3 | 4 | — |
| Methedrine | | 2 | 1 | — |

The bradycardia produced by neo-synephrine may result in a pulse rate as low as 30 a minute, according to Brunner and de Takats (1939), who have recorded partial heart block after administering the drug. No untoward effects of this nature were observed with neo-synephrine in this study.

Electrocardiograms were taken in four persons receiving methedrine, but no significant changes were observed. The cardiogram was normal the day after the author received a dose of 70 mg. intramuscularly in divided doses. Unfortunately there were no facilities for taking cardiograms with the other drugs.

Methedrine appears to be the only one of the four pressor drugs with a marked stimulating effect on the cortical centres. This is in the normal person. The effect was not noticed in patients submitted to surgical operations, being presumably neutralized by the premedication with morphine, the anæsthetic, and the post-operative morphine, which was usually given afterwards to patients undergoing major operations.

SUMMARY AND CONCLUSIONS

The clinical effectiveness of four pressor drugs, methedrine (pervitin, *d*-desoxyephedrine), paredrine, neo-synephrine, and pholedrine (veritol, paredrinol) has been examined. Each drug was tested on twenty patients showing a severe fall in blood pressure (to 80 mm. systolic pressure or to 10 mm. pulse pressure) during major surgical operations. The following were evaluated for each drug: optimum dose for a pressor response; maximum systolic and diastolic blood pressures, and rise in systolic and pulse pressure after giving the drug; effect on pulse rate; time taken for the drug to act; duration of action; and side effects on the cardiovascular system. On the basis of the results obtained the clinical effectiveness of the four pressor drugs examined is in this order: methedrine, paredrine, neo-synephrine, pholedrine. The principal criteria on which this opinion is based are: rise of systolic and pulse pressure when the drugs are given to surgical patients with a systolic blood pressure of 80 mm. or less; the speed and duration of action; and the relative freedom from side effects on the cardiovascular system.

The table below summarizes the results obtained.

| | | | Methedrine | Paredrine | Neo-synephrine | Pholedrine |
|-----------------------|-------|--|------------|-----------|----------------|------------|
| Satisfactory result | | | 18 | 8 | 7 | 4 |
| Unsatisfactory result | | | 2 | 12 | 13 | 16 |
| | | | <hr/> 20 | <hr/> 20 | <hr/> 20 | <hr/> 20 |

A result was rated as satisfactory if the systolic pressure remained above 100 mm. and the pulse pressure was not less than 30 mm. for a period of two hours or more.

Thanks are due to Mr. H. Dodd, Surgeon to the King George Hospital, Ilford, and Mr. Turner Warwick, Surgeon to the Middlesex Hospital, for their assistance and co-operation in this work.

REFERENCES

- Abbott, W. O., and Henry, C. M. (1937). *Amer. J. med. Sc.*, 193, 661.
 Altschule, M. D., and Gilman, S. (1939). *New Eng. J. Med.*, 221, 600.
 Altschule, M. D., and Iglauer, A. (1940). *J. Clin. Invest.*, 19, 497.
 Bittrich, N. M. (1939). *Anesth. & Analg.*, 17, 44.
 Brunner, R. S., and de Takats, G. (1939). *Surg. Gynec. Obst.*, 68, 1021.
 Difabio, F. X., Lawrence, J., and Ascione, J. F. (1941). *Anesth. & Analg.*, 20, 88.
 Dodd, H., and Merton, G. (1939). *Brit. J. Surg.*, 27, 78.
 Dodd, H. (1942). *Lancet*, 1, 498.
 — Prescott, F. (1943a). *Brit. med. J.*, 1, 345.
 — Prescott, F. (1943b). *Surg. Gynec. Obst.*, 79, 645.
 Iglauer, A., and Altschule, M. D. (1940). *J. Clin. Invest.*, 19, 503.
 Iglauer, A., and Molle, W. E. (1943). *Amer. Heart J.*, 26, 247.
 Johnson, C. A. (1937). *Surg. Gynec. Obst.*, 65, 458.
 Landau, E., Logue, V., and Kopelman, H. (1942). *Lancet*, 2, 210.
 Loman, J., *et al.* (1939). *Amer. Heart J.*, 18, 89.
 Lorhan, P. H., and Oliverio, R. M. (1938). *Anesth. & Analg.*, 17, 44.
 Lorhan, P. H., and Lalich, J. (1940). *Ibid.*, 19, 66.
 Myerson, A., and Loman, J. (1941). *New Eng. J. Med.*, 224, 412.
 Nathanson, M. H., *et al.* (1942). *Amer. Heart J.*, 24, 153.
 — Engelberg, H. (1942). *Proc. Soc. Exp. Biol. Med.*, 51, 239.
 Papper, E. M., *et al.* (1943). *J. Amer. med. Ass.*, 121, 27.
 Silvers, H. I., and Leonard, I. E. (1940). *Amer. J. Surg.*, 50, 79.

THE UNITY OF PAROXYSMAL TACHYCARDIA AND AURICULAR FLUTTER

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It is difficult in the common electrocardiogram of paroxysmal tachycardia to identify the auricular wave and to place it in relation to the ventricular complex. Accordingly the cardiographic classification for paroxysmal tachycardia based on the position of the P wave (deformed and preceding the R wave in the auricular type, succeeding or coinciding with the R in the auriculo-ventricular or nodal variety, and normal in the ventricular type) has not always been easy to follow in practice. Again, the record has often resembled that customarily called auricular flutter. As a rule the rhythm is readily distinguished from sinus tachycardia. Fortunately the treatment of paroxysmal tachycardia has not suffered from failure to understand its exact mechanism, since attention has usually been directed to the underlying heart condition, and digitalis and quinidine have been given a trial for the correction of the arrhythmia. Nonetheless, the actual mechanism of the attack has engaged the diligent search of many investigators, and a contribution to this subject is worth while.

The clear portrayal of auricular movements in auricular fibrillation (Fig. 1) in the right pectoral (CR₁) cardiogram (Evans, 1941) led me to apply chest leads to patients with paroxysmal tachycardia at the time of the attack. This paper gives the result of such cardiographic examination in 27 consecutive cases. The diagnosis of paroxysmal tachycardia was made when each patient told of periods of palpitation, starting abruptly and usually ending as suddenly after lasting a variable time during which the heart rate was very rapid, and when the limb lead cardiogram showed a high frequency of the ventricular beat, absence of sino-auricular rhythm, and auricular waves removed from their customary place in relation to the ventricular waves if decipherable at all. It is inevitable, therefore, that some of the tracings recorded here might be regarded by some as instances of auricular flutter, although they conform to the definition given above.

During the early part of the investigation three chest leads were used, namely, the right pectoral (CR₁), apical (IVR), and the posterior axillary (CR₇). When it became evident that the auricular waves did not show to better advantage in CR₇ than in the limb leads, it was discontinued as a routine test. Sometimes the auricular movements were depicted clearly in IVR, but they were best in CR₁ so this lead was taken in every patient.

RESULTS OF THE INVESTIGATION

The first tracings showed tachycardia with auricular beats twice as numerous as the ventricular, and when the CR₁ cardiogram was examined for the complete series it showed 2 : 1 A-V dissociation in every patient, although the limb lead had not often indicated this fact. For the purpose of analysis the cases may be separated into three groups according to the auricular and ventricular rates and the relationship of the auricular waves to the QRS

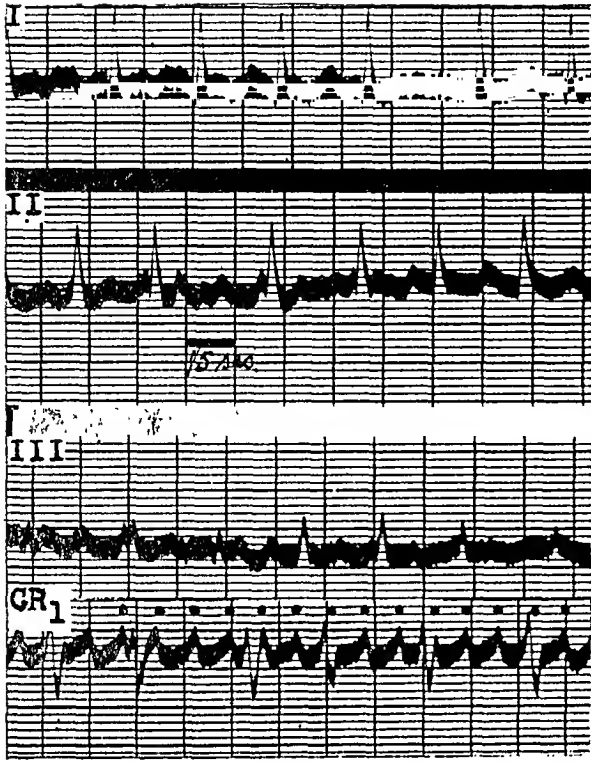


FIG. 1.—Auricular fibrillation; auricular rate (A.R.) 428, ventricular rate (V.R.) 150. Auricular waves in CR₁ show regular rhythm but slight irregularity in form. Male, aged 52, with cardiac infarction. In this and in other figures dots or arrows designate auricular beats.

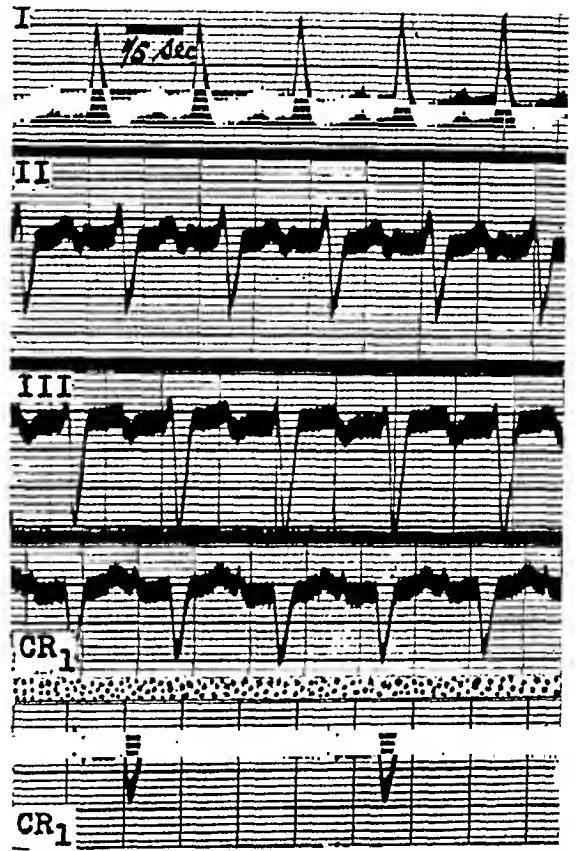


FIG. 2.—Sinus tachycardia resembling auricular tachycardia in limb leads. CR₁ recorded when pulse was rapid and again at normal rate, confirmed sinus rhythm. Flat T wave in second CR₁ from digitalis effect. Healthy female; aged 44, complaining of palpitation.

and T waves in the CR₁ lead. In one group, the rate was slow enough to allow both auricular waves to be shown. In another, the rate was more rapid so that one auricular wave was visible and the alternate one obscured by the coincidence of either the S or T wave of the ventricular complex. In the third group the rate was so rapid as to include and hide both auricular waves in the S and T waves respectively. Naturally the identification of A-V dissociation was not difficult in cases forming the first of these groups from reference to the limb lead cardiogram, but it was impossible in the other two groups. It is known that separation of the auricular and ventricular waves, by slowing the ventricular rate, cannot always be brought about by such measures as digitalization, quinidine therapy, and pressure on the carotid sinus, and in this series also such procedures commonly failed. It was possible, however, to identify the higher frequency of the auricular beats in the CR₁ cardiogram of each of the 27 cases in spite of the handicap of moderately severe tachycardia at times; the identification of the auricular waves in the second and third groups was helped by comparing the right pectoral tracing with one taken during normal rhythm either before or after the paroxysm. The value of this plan is illustrated in cardiograms from a patient thought to have paroxysmal tachycardia; during a spell of palpitation the rapid auricular waves were seen in CR₁ tracing (Fig. 2) to have the same rate as the ventricular waves. If an extra auricular wave had been present in this case it would have coincided with the S wave and produced an R¹ wave in CR₁ during the attack. Since the S wave has the same pattern during tachycardia and when the rate was normal, the rapid heart action arose from the sino-auricular node.

TABLE I

THE RIGHT PECTORAL ELECTROCARDIOGRAM (CR₁) IN 27 CONSECUTIVE CASES OF PAROXYSMAL TACHYCARDIA, AND IN 7 CASUAL EXAMPLES OF ESTABLISHED AURICULAR FLUTTER

| Initials or Case No. | Age | Nature of underlying heart disease | Auricular rate | | Ventricular rate | | Distinctive features of the right pectoral electrocardiogram | Particular ventricular wave obscuring auricular wave |
|----------------------|-----|------------------------------------|----------------|------------|------------------|------------|--|--|
| | | | Individual | Group † | Individual | Group | | |
| F. A. | 61 | Hypertension | 280 | Variable | 23 | Under 100 | 3 : 1 (or greater) A-V dissociation. Three or more consecutive auricular waves outside ventricular waves | — |
| E. C. | 62 | Hypertension | 280 | | 34 | | | — |
| E. D. | 62 | Healthy | 230 | | 40 | | | — |
| A. E. | 43 | Mitral stenosis | 328 | | 50 | | | — |
| P. B. | 70 | Healthy | 292 | | 73 | | | — |
| F. S. | 57 | Hypertension | 300 | | 75 | | | — |
| H. D. | 50 | Mitral stenosis | 236 | | 80 | | | — |
| 1 | 46 | Mitral stenosis | 210 | 200 to 260 | 105 | 100 to 130 | 2 : 1 A-V dissociation. Both auricular waves outside ventricular waves | — |
| 2 | 60 | Mitral stenosis | 212 | | 106 | | | — |
| 3 | 21 | Healthy | 240 | | 120 | | | — |
| 4* | 69 | Hypertension | 254 | | 127 | | | — |
| 5* | 28 | Mitral stenosis | 256 | | 128 | | | — |
| 6 | 68 | Hypertension | 260 | 260 to 400 | 130 | 130 to 200 | 2 : 1 A-V dissociation. Alternate auricular waves within a ventricular wave | S |
| 7* | 58 | Mitral stenosis | 264 | | 132 | | | S |
| 8 | 65 | Mitral stenosis | 264 | | 132 | | | S |
| 9 | 53 | Mitral stenosis | 282 | | 141 | | | S |
| 10 | 52 | Mitral stenosis | 282 | | 141 | | | T |
| 11 | 63 | Hypertension | 292 | | 146 | | | S |
| 12 | 58 | Mitral stenosis | 300 | | 150 | | | S |
| 13 | 38 | Healthy | 308 | | 154 | | | S |
| 14 | 34 | Healthy | 320 | | 160 | | | S |
| 15* | 61 | Hypertension | 332 | | 166 | | | T |
| 16* | 50 | Mitral stenosis | 338 | | 169 | | | T |
| 17 | 64 | Healthy | 342 | | 171 | | | S |
| 18 | 53 | Cardiac infarction | 364 | | 182 | | | S |
| 19* | 59 | Cardiac infarction | 376 | | 188 | | | T |
| 20 | 19 | Healthy | 380 | | 190 | | | S |
| 21 | 50 | Healthy | 400 | Over 400 | 200 | Over 200 | 2 : 1 A-V dissociation. Both auricular waves within ventricular waves | S and T |
| 22 | 22 | Healthy | 400 | | 200 | | | S and T |
| 23* | 55 | Cardiac infarction | 400 | | 200 | | | S and T |
| 24 | 25 | Healthy | 422 | | 211 | | | S and T |
| 25 | 54 | Mitral stenosis | 434 | | 217 | | | S and T |
| 26 | 42 | Mitral stenosis | 434 | | 217 | | | S and T |
| 27 | 42 | Healthy | 496 | | 248 | | | S and T |

* Denotes that the patient has since died.

† The arrangement in four groups is based on the auricular rate and the degree of A-V dissociation, both of which determine the conspicuity of the auricular waves in the cardiogram.

Auricular Tachycardia of High Rate

When the ventricular rate was 100 to 130 a minute and the auricular rate 200 to 260, both auricular waves were visible outside the QRS and T waves, so that 2 : 1 A-V dissociation was obvious. Five of the 27 cases belong to this group (Cases 1 to 5; Fig. 3, 4, 5, and 6). The cardiogram in one case (Fig. 3) emphasizes how the clear portrayal of the auricular waves depends on the rate; thus in the CR₁ lead both auricular waves were visible when the auricular rate was 210 a minute, but when the rate was 300, one auricular wave became obscured within the S wave. The tracing from another patient (Fig. 7) similarly shows how the hidden auricular waves at high rate are unmasked when the A-V dissociation changes from 2 : 1 to 3 : 1 or 4 : 1. Three of the five patients had mitral stenosis, one was otherwise healthy and the other had hypertension and heart failure. Two have since died and three survive. Quinidine produced no effect on the arrhythmia in two of the patients in whom it was tried; in another the rhythm changed to auricular fibrillation and later to normal rhythm during quini-

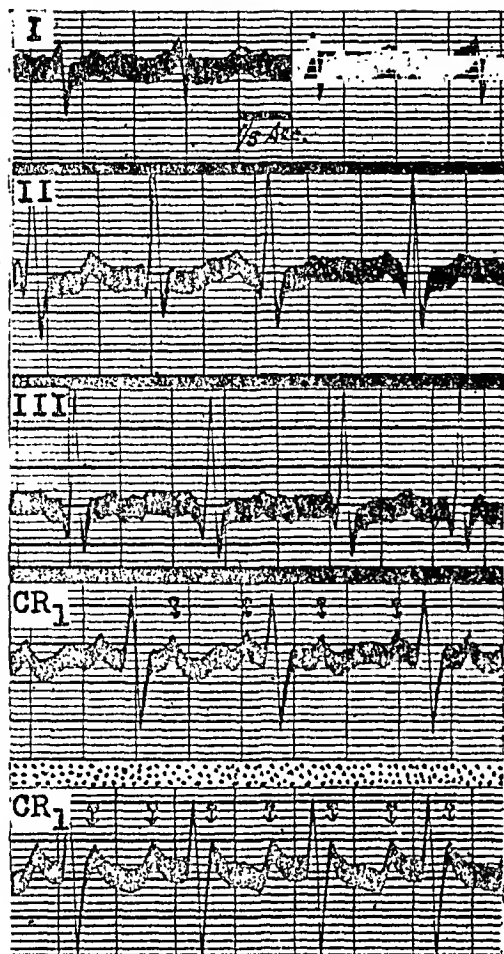


FIG. 3.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 210. Both auricular waves outside ventricular waves. Second CR₁ shows a more rapid rate (A.R., 300) so that one auricular wave is now obscured by S wave. Case 1.

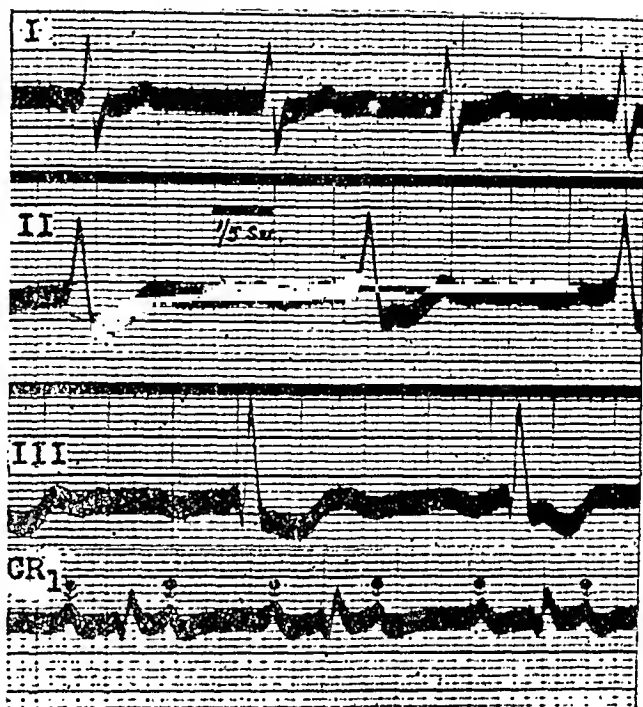


FIG. 4.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 122. Both auricular waves outside ventricular waves. Case 2.

dine therapy. In three patients digitalis changed the arrhythmia into auricular fibrillation which persisted in two during continued digitalization; in another, digitalis established normal rhythm directly.

Auricular Tachycardia of Higher Rate

When the ventricular rate was 130 to 200 a minute and the auricular rate was 260 to 400, alternate auricular waves were hidden within the S (in 11 cases) or T waves (in 4 cases) of the ventricular complex, and the 2 : 1 A-V dissociation could not be made out in the limb lead tracing, but it was made apparent in the CR₁ record. Fifteen of the 27 cases belong to this group (Cases 6 to 20; Fig. 7 to 14 and 21). When the auricular wave coincided with the S it produced an upright extension of the S in CR₁ above the isoelectric level to form an R¹ wave, and whenever the same lead was recorded in normal rhythm this extra wave was absent. Manifestly this change is not the outcome of tachycardia alone, but is an expression of the presence of an auricular wave, because in rapid tachycardia of sinus origin (Fig. 2) the R¹ is not present. Six of the patients had mitral stenosis, three had hypertension, two had cardiac infarction, and four were healthy. Four have since died and eleven survive. Quinidine was not tried in 8 patients, but in 6 it had no effect, and in another it produced normal rhythm. Digitalis was not tried in 7 patients, but in 2 it had no effect, and in 6 it changed the rhythm into auricular fibrillation which in 2 reverted to normal rhythm.

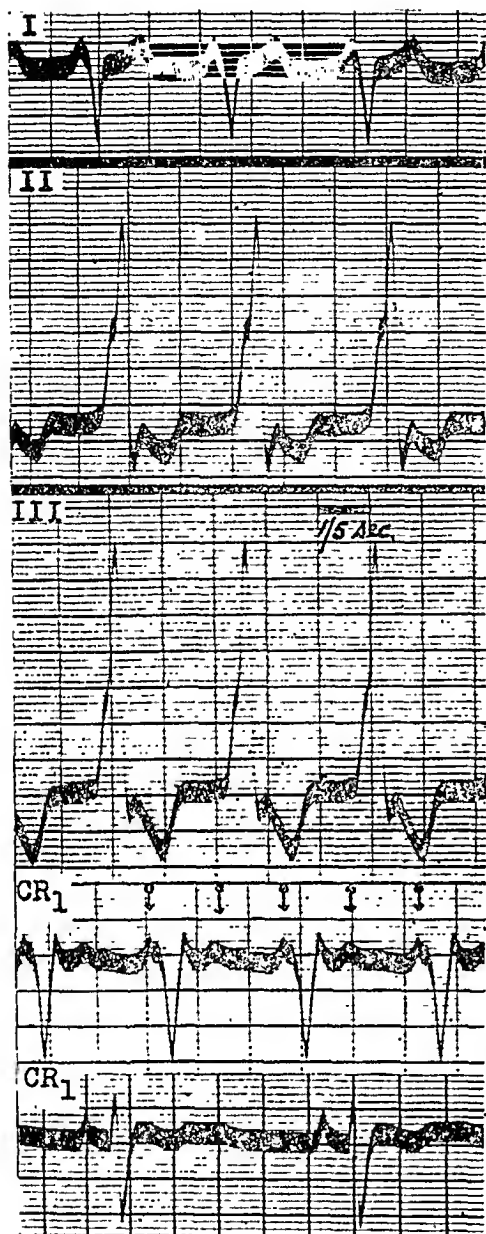


FIG. 5.—Auricular tachycardia with 2:1 A-V dissociation; A.R., 240. Both auricular waves outside ventricular waves. CR₁ in normal rhythm for comparison showing inversion of T wave. Case 3.

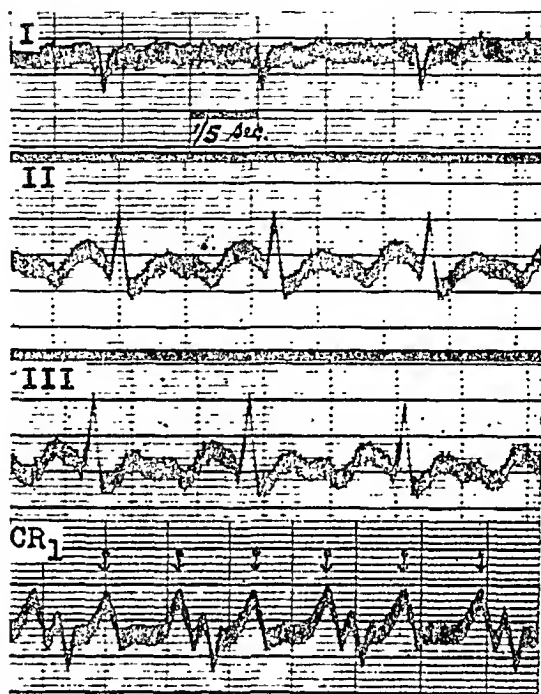


FIG. 6.—Auricular tachycardia with 2:1 A-V dissociation; A.R., 256. Both auricular waves outside ventricular waves. Case 5.

Auricular Tachycardia of Very High Rate

When the ventricular rate was over 200 a minute and the auricular rate over 400, both auricular waves were obscured within the S and T waves of the ventricular complex. Even at this high rate the auricular beats were demonstrated by a chest lead cardiogram, and best in CR₁. Seven of the 27 cases belong to this group (Cases 21 to 27; Fig. 15 and 16). Two patients had mitral stenosis; another had cardiac infarction and died when the attack was three days old; four were otherwise healthy. Quinidine was not given to two patients, but in four it failed either to prevent or relieve the attacks; in another it succeeded. Digitalis also had no effect when tried in three of these patients, but it stopped the attack in one other.

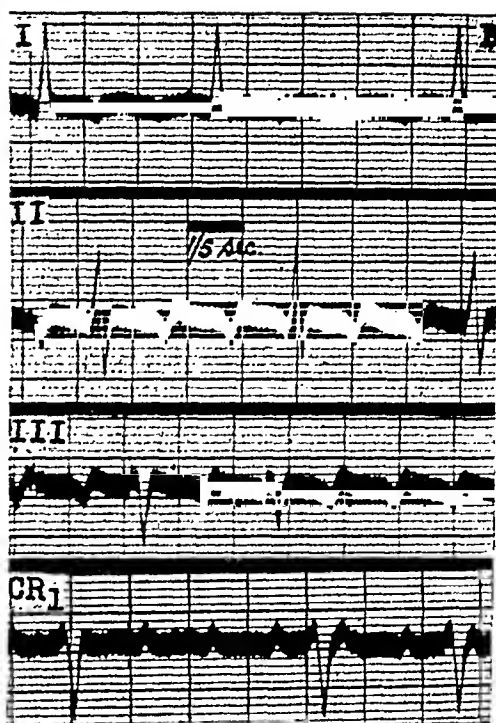
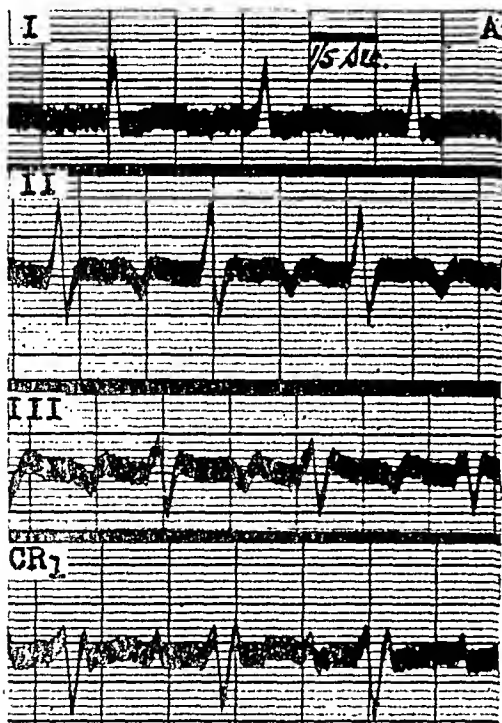


FIG. 7.—Auricular tachycardia with A-V dissociation. In (A) there is 2 : 1 dissociation and A.R. is 260, alternate auricular waves within S. Appearance of tracing suggests flutter. In (B) A.R. is still 260, but A-V dissociation is 3 : 1 and 4 : 1 as a result of reduction in ventricular rate by digitalization. Tracings emphasize effect of ratio of A-V dissociation in obscuring auricular waves in addition to effect of rate. Case 6.

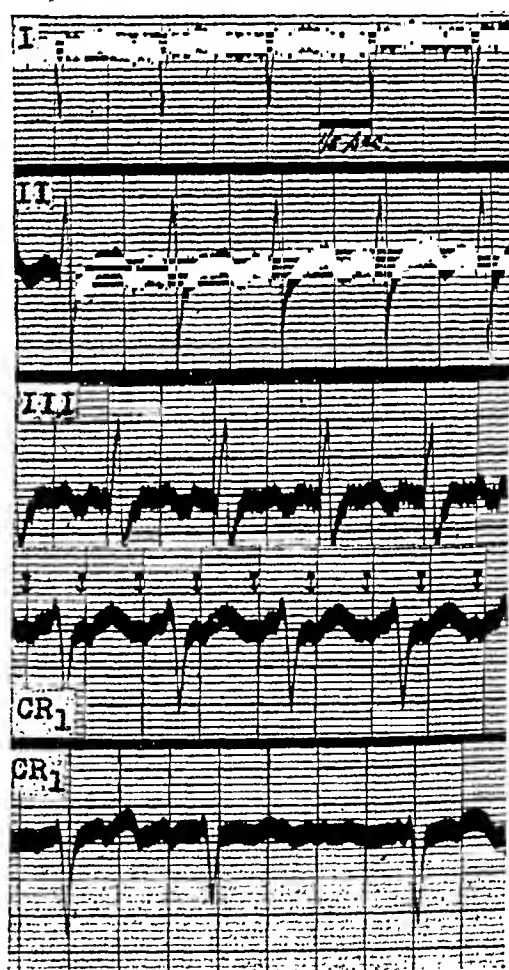
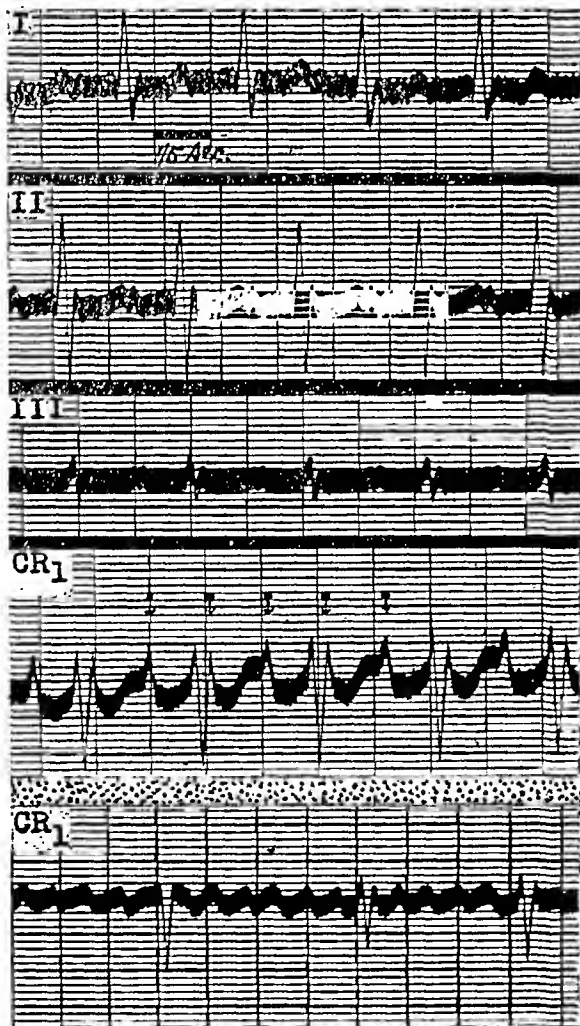


FIG. 8.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 264. Alternate auricular waves within S wave producing an R^1 wave. CR₁ in auricular fibrillation for comparison showing disappearance of R^1 . Case 7.

FIG. 9.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 300. Alternate auricular waves within S wave. CR₁ in auricular fibrillation for comparison. Case 12.

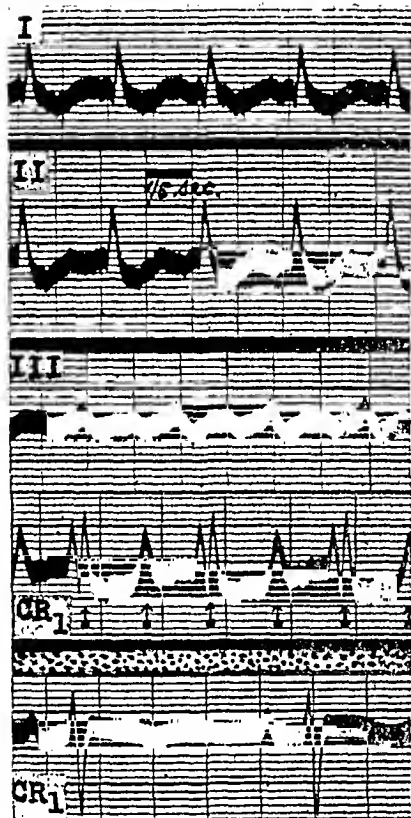


FIG. 10.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 264. Alternate auricular waves within S wave producing an R' wave in CR_1 . CR_2 in normal rhythm for comparison showing disappearance of R' wave. Case 8.

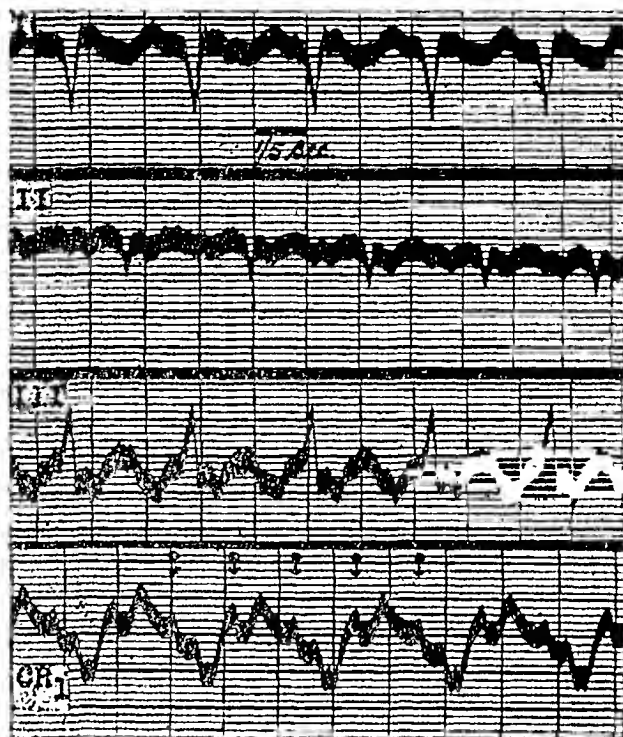


FIG. 11.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 282. Alternate auricular waves within S wave producing an R' wave in CR_1 . Case 9.

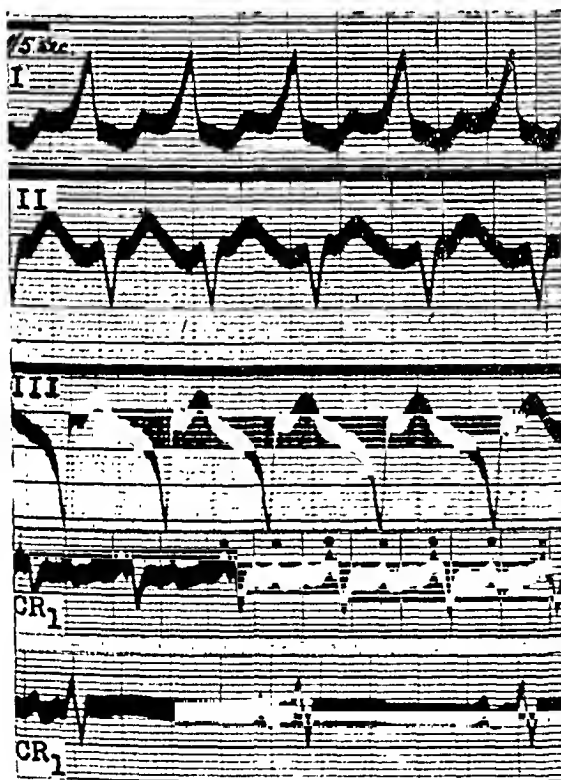


FIG. 12.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 282. Alternate auricular waves within T wave. CR_1 in normal rhythm for comparison. Case 10.

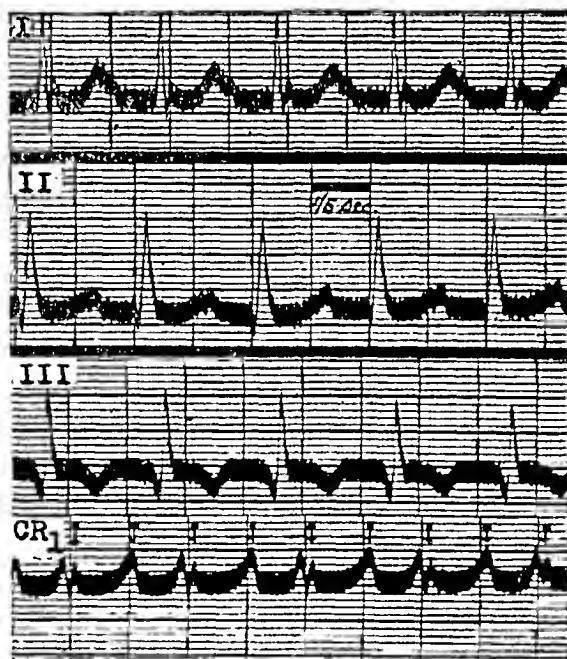


FIG. 13.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 308. Alternate auricular waves within S wave producing an R' wave in CR_1 . Case 13.

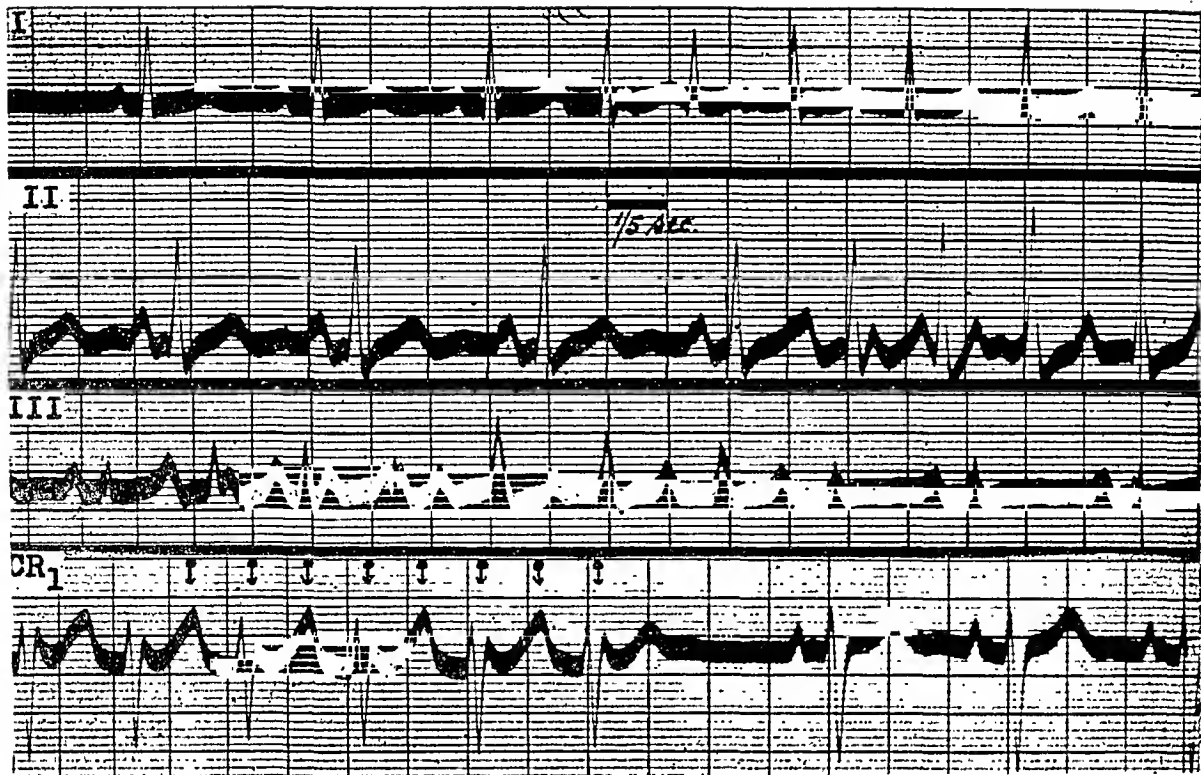


FIG. 14.—Short paroxysms of auricular tachycardia in each lead showing 2 : 1 A-V dissociation during such periods when auricular rate was 320. An R^1 and a tall and peaky T wave in CR_1 produced by auricular waves, have disappeared during normal rhythm. Case 14.

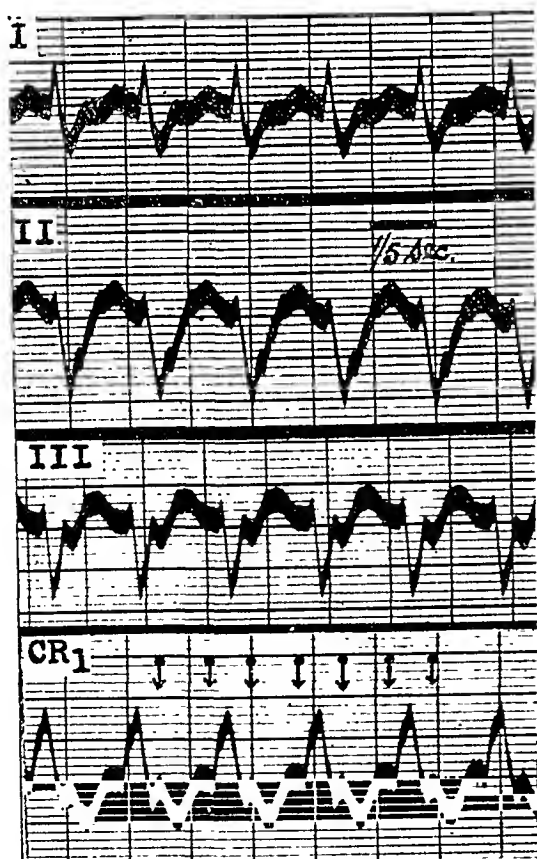


FIG. 15.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 400. Auricular waves within S and T waves. Case 22.

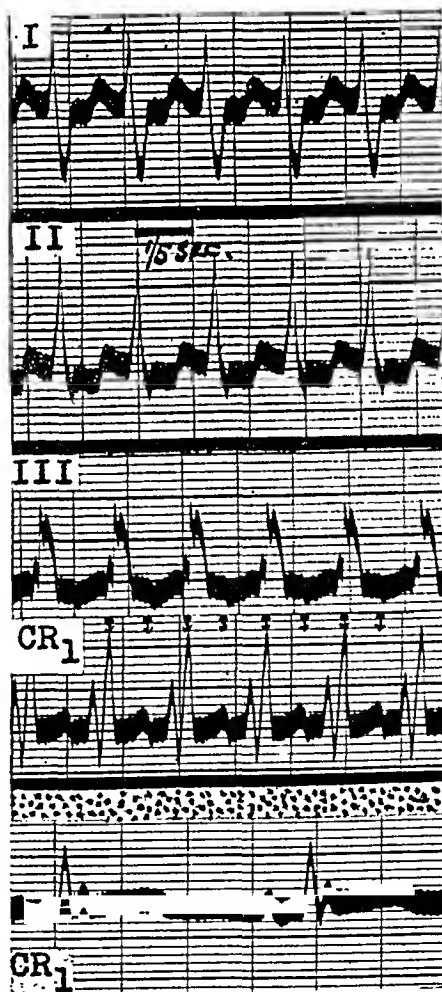


FIG. 16.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 496. Auricular waves within S and T waves. CR_1 in normal rhythm for comparison. Case 27.

Auricular Tachycardia with Slow Ventricular Rate

For comparison with the series of 27 cases of paroxysmal tachycardia, I have collected cases that had cardiograms showing a rapid and regular auricular action as an established arrhythmia but with a much slower ventricular rate (under 100 a minute). From among these, 7 have been listed in Table I as being representative of a larger group. The auricular rate varied from 230 to 330 a minute and A-V dissociation was present. The ventricular rate varied from 20 to 100, and at least three consecutive auricular waves appeared outside the ventricular complexes. Rarely, the ventricular beats were regular and very slow because of complete heart block (Fig. 17). In other cases the ventricular beats were more frequent (Fig. 18 and 19) and occasionally occurring irregularly (Fig. 20). The auricular waves in II and III of the limb lead cardiogram from patients in this group conformed to the type customarily regarded as auricular flutter, and the intervals between the auricular waves in CR₁ were at the isoelectric level.

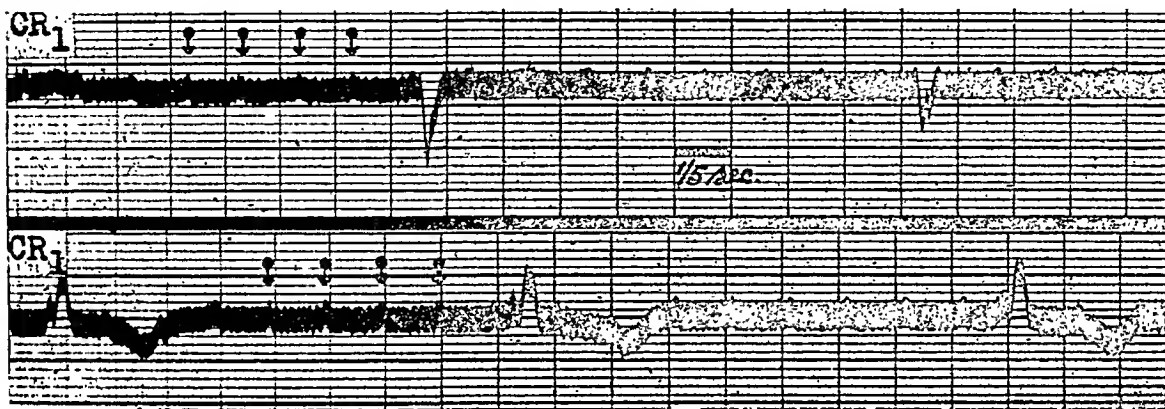


FIG. 17.—Auricular tachycardia with complete A-V dissociation; A.R., 280; V.R., 23. Several consecutive auricular waves appear outside ventricular complexes which in first CR₁ are of right, and in second CR₂ of left bundle branch type. Female, aged 62, with hypertension.

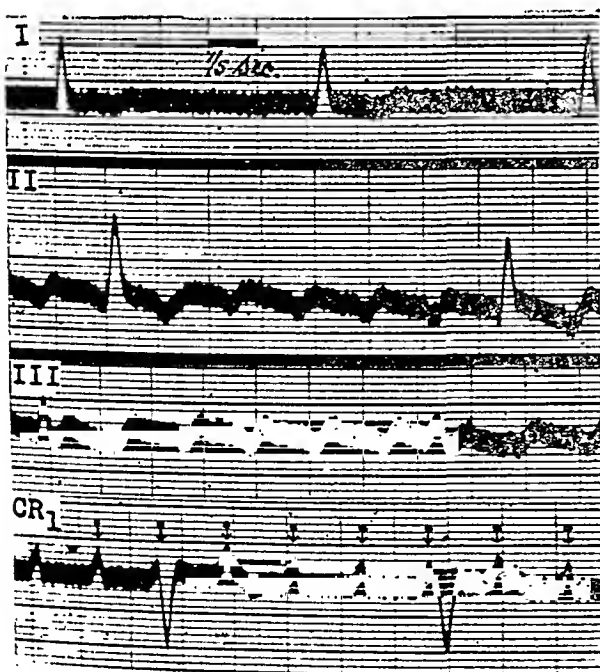


FIG. 18.—Auricular tachycardia with A-V dissociation; A.R., 230; V.R., 40. Three or more consecutive auricular waves outside ventricular waves. Interauricular periods isoelectric in CR₁. Male, aged 62, without heart disease.

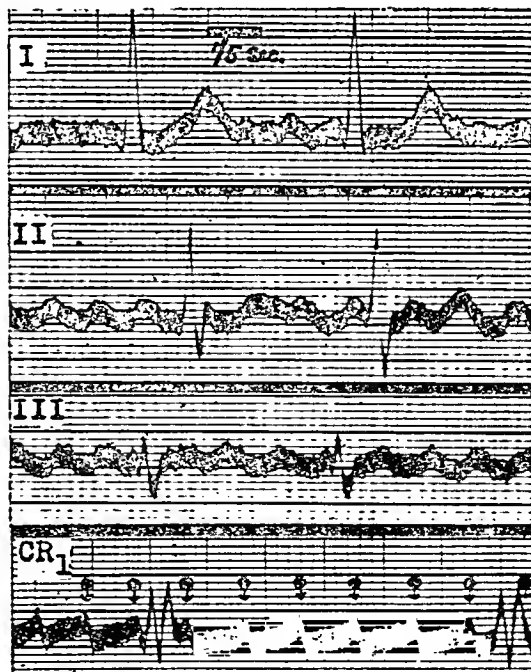


FIG. 19.—Auricular tachycardia with A-V dissociation; A.R., 328; V.R., 50. Three or more consecutive auricular waves outside ventricular waves. Male, aged 43, with mitral stenosis.

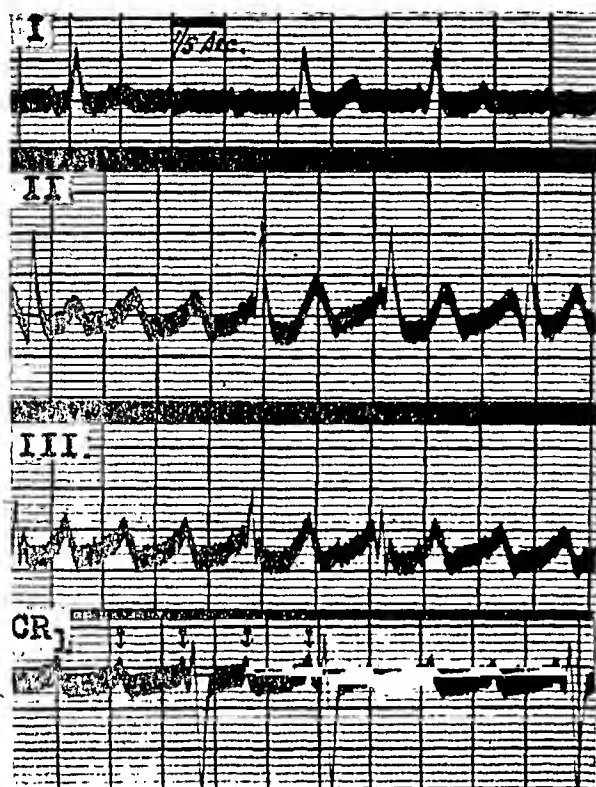


FIG. 20.—Auricular tachycardia with A-V dissociation; A.R., 236; V.R., 80. Three or more consecutive auricular waves outside ventricular waves. Male, aged 50, with mitral stenosis.

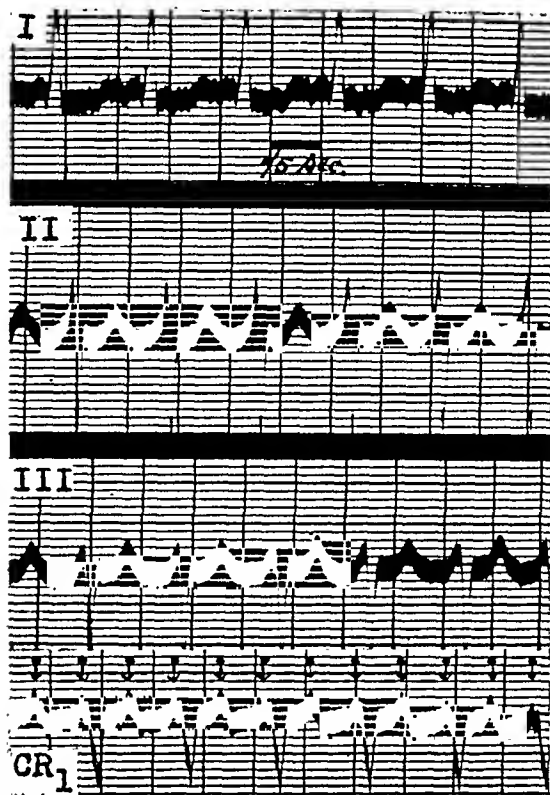


FIG. 21.—Auricular tachycardia with 2:1 A-V dissociation; A.R., 338. Alternate auricular waves within T wave. Case 16.

A-V Dissociation in Paroxysmal Tachycardia

Many instances of heart block have been reported in cases with paroxysmal tachycardia. Lewis (1910a) found that paroxysmal tachycardia frequently followed the ligation of a coronary artery in the experimental animal; it developed spontaneously whenever there was great acceleration of the ventricular rate. In 12 such instances heart block was noticed, but the auricular rate was half that of the fast ventricular rate. Later Lewis (1910b), recording simultaneous curves from auricle and ventricle by myocardiographic levers, alongside an electrocardiogram, demonstrated 2:1 A-V dissociation at high rates. In another paper Lewis (1912) described seven such cases in man; in four of them the auricular and ventricular rates were 300 and 150, 320 and 160, 224 and 112, and 334 and 167, respectively. In the first case the true interpretation of the cardiogram during tachycardia became possible by comparing it with later tracings recorded when the ventricular rate had been halved by digitalis therapy. The cardiogram of another case was shown in a paper by Mackenzie (1910) (his Fig. 56) as an example of paroxysmal tachycardia, but without reference to the 2:1 A-V dissociation which it demonstrated. Sprague and White (1925) said that the essential feature of auricular paroxysmal tachycardia, was that the auricles beat regularly and rapidly at a constant rate under the control of an abnormal pacemaker, and that the ventricles maintained an equally rapid rate, contracting in response to all the stimuli; there was no block between the chambers. They found, however, among 56 cases of paroxysmal tachycardia where electrocardiograms were recorded during attacks, 3 instances which were unusual in that they showed heart block. The auricular and ventricular rates in the three cases were 240 and 120, 220 and 110, and 190 and 95, respectively. Single instances of heart block in paroxysmal tachycardia have been reported by Dock (1928), Laubry and Deglaude (1932), Carr (1932), Géraudel (1937), Maddox (1937), Fine and Miller (1940), Tanney and Lilienfeld (1942), and by Parsons (1943).

An important contribution to the incidence of heart block in paroxysmal tachycardia was made by Brown (1936), who recorded an œsophageal electrogram, at the level of the left auricle, in two patients during the attack. Both showed 2 : 1 A-V dissociation. Brown said that his two cases provided evidence that A-V block does occur in auricular paroxysmal tachycardia, and that the auricular rate in this condition may rise certainly to 300 and very probably as high as 428 beats a minute. Barker, Wilson, Johnson, and Wishart (1943) reviewed 17 previously reported cases of auricular paroxysmal tachycardia associated with heart block, and described 18 cases of their own; 6 of their published cardiograms would be regarded by some as auricular flutter. They mentioned that in such cases the attacks often lasted longer than in the common type although they reported notable exceptions. The auricular rate was usually between 165 and 200 a minute, but much higher rates were also met with. They also noticed that patients of this group were often resistant to treatment. Speaking of cardiographic diagnosis they emphasized the difficulty of identifying the nature of the arrhythmia when the P waves were small or indistinct in the standard limb lead cardiogram. In such circumstances they mentioned that chest leads might prove helpful and they used it in 6 of their cases. A notable addition to the number of recorded cases of paroxysmal tachycardia with A-V block has been made by Decherd, Herrmann, and Schwab (1943), who described 40 patients showing this combined arrhythmia. It is not known whether some of their cases showed tracings that might be regarded as typifying auricular flutter because they did not publish the three limb leads in any. Their experience led them to believe that the incidence of A-V block in paroxysmal tachycardia was much commoner than hitherto suspected. Death occurred in 22 cases (55 per cent) during their stay in hospital, and they concluded that the prognosis was serious in this group of patients; only 2 cases in the series were without heart disease, while 35 showed congestive heart failure even before the appearance of the arrhythmia. Decherd and his colleagues believed that the high incidence of heart disease and medication with quinidine or digitalis had contributed to the incidence of A-V block in their patients. The grade of block varied, but 2 : 1 was commonest and was recorded in 21 patients; it was 4 : 3 or 3 : 2 in 18 cardiograms which included three chest records.

THE RELATIONSHIP BETWEEN AURICULAR TACHYCARDIA AND AURICULAR FLUTTER

During paroxysmal tachycardia it is not possible on clinical grounds to tell whether the arrhythmia takes the form of auricular tachycardia or auricular flutter, although auricular flutter is favoured if the attack is prolonged. The difficulty of cardiographic interpretation when the rate is rapid is real. If A-V dissociation became common to auricular tachycardia as well as to flutter, the pertinent question as to the difference between them would need an answer. The inclusion by Barker and his colleagues (1943) of 6 cardiograms that might be regarded by many as examples of auricular flutter, in a paper on paroxysmal tachycardia, provides another reason for examining the subject. Again, in their discussion of a paper on A-V dissociation in 40 cases of paroxysmal tachycardia Decherd *et al.* (1943) say that it must be explicitly stated that we do not possess absolute criteria for sharp differentiation between auricular tachycardia and flutter. Thus, the identification marks customarily applied to each in the past require to be examined again, and decision taken on their specificity for one type or their common application to both. The several characteristics of the two forms of arrhythmia will now be examined.

Historical. The term flutter was first used by MacWilliam (1887) when he wrote about the fibrillar contraction of the heart in the experimental animal. He stated that the phenomena resulting from faradic stimulation of the auricles differed in many respects from those witnessed in the ventricles. The application of the current set the auricles into a rapid flutter, the rapidity of which depended largely on the excitability of the auricular tissue and the strength of the current employed. He described the movements as regular and consisting of a series of

contractions originating in the stimulated area and thence spreading over the rest of the tissue. The movement showed no sign of incoordination, and it looked like a rapid series of contraction waves spreading over the auricular walls. MacWilliam did not tell of the ventricular response to such movements, neither did he record them instrumentally, but only interpreted his visual impression. When Jolly and Ritchie (1910) reported a case of rapid and regular action of the auricle (250 to 300 a minute) they applied the term auricular flutter to the electrocardiogram because it seemed to represent the phenomenon observed and described by MacWilliam during experimental auricular tachycardia. After that the term came into common use.

Duration of the Attack. Auricular flutter, although not uncommonly presenting as brief paroxysms, is more often met with as an established condition. Parkinson and Bedford (1927) stated that flutter in paroxysms constituted a special variety of paroxysmal tachycardia. In about 25 per cent of cases, flutter was purely paroxysmal and was then frequently associated with paroxysms of fibrillation. Auricular tachycardia, on the other hand, although sometimes maintained for long periods, is usually confined to brief attacks. In addition to finding exceptions in each group, I found this distinction between the two kinds of arrhythmia to be fairly closely related to the rate. Thus, cases that show the relatively longer paroxysms of tachycardia have a less rapid auricular rate (300 or less a minute) and often a ratio of A-V dissociation greater than 2 : 1.

The Auricular Rate. A high auricular rate (about 300 a minute) has been regarded as characteristic of auricular flutter, serving to distinguish it from auricular paroxysmal tachycardia with its slower rate of about 160 to 240 a minute. But now that A-V dissociation has been shown to occur in auricular tachycardia, and to be an invariable feature of it in the cases reported here, the high auricular rate may prove to be common to both arrhythmia, at least in most cases. Further, the auricular rate in auricular tachycardia is quite stable as in flutter and is not often altered appreciably by rest, posture, emotion, or exercise.

Response to Treatment. Pressure on the carotid sinus in patients in this series never had the effect of slowing either auricular or ventricular rate sufficiently to separate the auricular and ventricular complexes in the cardiogram. Only once did this manœuvre stop an attack, in a patient in whom the paroxysms were very brief. Parkinson and Nicholl (1922) tried quinidine in six cases of paroxysmal tachycardia, in two of which the attacks were prolonged; in none were they satisfied that quinidine had a beneficial effect. Barker, Wilson, and Johnston (1943) stated that quinidine slowed the heart rate in paroxysmal tachycardia as it did the circus movement in flutter. Quinidine was tried in 15 of the 27 cases; in 12 it had no effect; in one it produced auricular fibrillation; in two it restored normal rhythm. In none did quinidine prevent the return of the attacks. The conversion of paroxysmal tachycardia into auricular fibrillation by digitalis has been reported by Lewis (1912), and by Barker, Wilson, Johnston, and Wishart (1943). Digitalis was tried in 16 of my cases; in 6 it had no effect; in 7 it changed the rhythm into auricular fibrillation, and later normal rhythm was resumed in 3 of these; in 3 digitalis restored normal rhythm directly. Such effects are also witnessed in the treatment of auricular flutter with quinidine and digitalis. Quinidine, or quinidine and digitalis alternately, was tried by Parkinson and Bedford (1927) in the treatment of 27 cases of auricular flutter. They found that digitalis removed flutter far more often than did quinidine. Digitalis alone restored normal rhythm in over a third of the cases, and in another third it induced fibrillation. Quinidine converted flutter directly into normal rhythm in about one case in five; it often cut short paroxysms of flutter, though continued small doses did not entirely prevent their recurrence. Where digitalis had left fibrillation, quinidine sometimes converted this into normal rhythm. Bourne (1933) reported a return to normal rhythm in two out of three cases of paroxysmal tachycardia during digitalization. Campbell and Suzman (1934) observed a case of auricular flutter and rheumatic heart disease for six years; while the patient was taking

the same dose of digitalis as had been dispensed over two years, normal rhythm was restored, but only for three months. In another case of auricular flutter without heart disease, Lewis (1937) watched the arrhythmia continue, without impairment of the heart's efficiency for 24 years; digitalization had proved of no avail.

A-V Dissociation. Hitherto A-V dissociation has been regarded as typical of auricular flutter and a rare happening in paroxysmal tachycardia, but this distinction can no longer apply now that it has been found in so many instances of auricular tachycardia; 17 cases by various authors; 16 by Barker *et al.* (1943); 40 by Decherd *et al.* (1943); and in every case in this series of 27.

Presence of Heart Disease. Out of 100 cases of paroxysmal tachycardia reported by Campbell and Elliott (1939) 55 were healthy. Among 52 cases of auricular flutter examined by Parkinson and Bedford (1927) there were only 5 without heart disease. Another 7 such cases were reported by Orgain, Wolff, and White (1936). Among my 27 cases of paroxysmal tachycardia, there were 11 with mitral stenosis, 4 with hypertension, 3 with cardiac infarction, and 9 who were healthy.

Mechanism. When Mines (1913) described circus rhythm he suggested that it might be responsible for some cases of paroxysmal tachycardia. From their observations on the effects of quinidine upon paroxysms, Iliescu and Sebastiani (1923) believed that auricular tachycardia was due to circus contraction. Lewis (1925) pointed out that the total amount of auricular muscle was not sufficiently large to accommodate a circus mechanism at known rates of conduction in auricular muscle and with cycles as long as those which occur in auricular paroxysmal tachycardia. Now that a more rapid auricular rate has been found common in auricular tachycardia, a circus mechanism cannot be excluded on that ground. This problem has been studied again by Barker, Wilson, and Johnston (1943), and they found strong evidence that auricular paroxysmal tachycardia is caused by circus rhythm involving one of the specialized nodes, either the sino-auricular or auriculo-ventricular node.

Interchangeability of Rhythm. It is known (Lewis, 1912; Parkinson and Matthias, 1915; and Carr, 1932) that paroxysmal auricular tachycardia may change spontaneously to auricular flutter or fibrillation, and flutter or fibrillation may change to paroxysmal tachycardia. This suggests that the conditions are related one to another.

Auricular Deflections and Interauricular Period. In every case in this series the auricular wave was upright in the right pectoral lead suggesting that the ectopic impulse had its origin near the sino-auricular node. It has been held that the auricular movements depicted in the cardiogram of auricular flutter are continuous and that the record does not show any pauses at the isoelectric level between the beats. This is usually true for the limb leads II and III, but it is not true for œsophageal and certain chest leads. Thus in cases that showed such continuous auricular waves in leads II and III, there were usually quiescent intervals between auricular waves at the isoelectric level in the CR₁ cardiogram (Fig. 17, 18, and 20). Similar silent pauses were present in all the other examples of auricular tachycardia. The high auricular and ventricular rate in auricular tachycardia has made the cardiographic diagnosis of auricular flutter less frequent, for the ventricular waves have obscured the pattern of the auricular waves in the limb leads. This is well illustrated in a case of paroxysmal auricular tachycardia reported by Parkinson and Matthias (1915). In their Fig. 4 a sudden infrequency of the ventricular beats has unmasked four consecutive auricular beats which appear typical of those customarily regarded as auricular flutter; the auricular rate of 240 a minute continued as in the earlier part of the record. The same unmasking of auricular beats by a slower ventricular rate is illustrated in Fig. 7 of the present paper. Barker, Wilson, and Johnston (1943) have pointed out that complete separation of the auricular deflections by isoelectric periods is consistent with the continuation of activity during circus movement, provided the circus path traverses either the sino-auricular or auriculo-ventricular node. These authors have postulated that such circumstances operate in paroxysmal auricular tachycardia.

DISCUSSION

There has been no lack of research into paroxysmal tachycardia; indeed the medical literature over a period of 30 years records many observations on the behaviour of the human heart during the attack and under the influence of treatment intended to abort the attack. But the outcome of past research has not been to agree on the nature and mechanism of this rapid heart action. The reproduction of a comparable state in the experimental animal has been difficult so that little help has come from that source. Clinically the description of the attacks has been accepted from patients examined in the intervals between the attacks and in the absence of cardiographic observations during a paroxysm of tachycardia. Gradually, the similarity of paroxysmal tachycardia and auricular flutter has been noticed clinically and cardiographically, and since it has now been shown that A-V dissociation is a common feature of paroxysmal tachycardia as well as of flutter, the common design of the two forms of arrhythmia appears more real. Should this uniformity receive emphasis by the results of further investigation, it will simplify the clinical and cardiographic diagnosis, and allow attention to be directed to a trial of digitalis and quinidine for aborting the attack, and otherwise to consider prognosis and additional treatment in relation to the presence and nature of the underlying heart disease.

If the presence of A-V dissociation in paroxysmal tachycardia, found in every patient in this series, is confirmed by future cardiographic investigation, the terms paroxysmal tachycardia and auricular flutter will have become interchangeable.

Thus, *auricular flutter* is paroxysmal tachycardia in which a moderate auricular rate (200 to 260) facilitates the finding of A-V dissociation in the cardiogram, because both auricular waves are separate from the two main waves of the ventricular complex; a greater A-V dissociation from slowing of the ventricular rate shows three or more consecutive auricular waves outside the ventricular complex even at higher auricular rates.

Again, *paroxysmal tachycardia* is auricular flutter where the more rapid auricular rate (260 to 500) prejudices the recognition of the auricular waves hidden within the ventricular complexes and hinders the discovery of a 2 : 1 A-V dissociation. In such circumstance comparison of a right pectoral cardiogram in an attack with one in normal rhythm will help in deciphering the nature of the arrhythmia.

From the clinical standpoint the attacks in the first group are inclined to be longer, more amenable to digitalis influence, and more certain to be associated with heart disease. But to each of these three distinctive features there are common exceptions.

CONCLUSION

A right pectoral electrocardiogram (CR₁) demonstrated the presence of A-V dissociation, usually 2 : 1, in 27 consecutive cases of paroxysmal tachycardia. Further investigation is necessary before assigning this feature to all or to the majority of such patients.

In the meantime the finding suggests the common unity of paroxysmal tachycardia and auricular flutter, with auricular tachycardia as the essential mechanism of each, showing variations in rate and in the degree of A-V dissociation.

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ABSTRACT OF CASE NOTES

Case 1. A man, aged 47, with mitral stenosis. Complained of shortness of breath and attacks of palpitation. Systolic and mid-diastolic murmurs in mitral area. No clinical evidence of heart failure. Cardioscopy showed moderate enlargement of heart from mitral stenosis, and slight pulmonary congestion. Electrocardiogram (EC.) shown in Fig. 3.

Quinidine failed to prevent or abort attacks. Digitalis converted arrhythmia into auricular fibrillation.

Case 2. A woman, aged 60, with mitral stenosis. Complained of shortness of breath and palpitation. Clinical evidence of mitral stenosis with much cardiac enlargement, and failure. Cardioscopy showed aneurysmal dilatation of left auricle and pulmonary congestion.

When attack of tachycardia persisted (Fig. 4), digitalis converted it into auricular fibrillation. Quinidine was never tried.

Case 3. An otherwise healthy man, aged 21. Complained of palpitation for over three years. Latterly attacks had lasted for some months. No abnormal signs on clinical or cardioscopic examination. EC. shown in Fig. 5.

Digitalis restored normal rhythm in four days. Quinidine was not tried.

Case 4. A man, aged 69, with hypertensive heart failure. Admitted to hospital because of nocturnal breathlessness. Blood pressure 170/110. Triple rhythm from addition of fourth heart sound, and other signs of left ventricular failure. Diffuse chronic bronchiectasis. Developed bronchopneumonia and tachycardia. EC. showed auricular tachycardia with 2:1 A-V dissociation; A.R., 254; both auricular waves outside ventricular waves.

Quinidine changed rhythm to auricular fibrillation and to normal rhythm. Further attacks of tachycardia uninfluenced by quinidine or digitalis, and patient died.

Case 5. A woman, aged 28. Attacks of tachycardia and symptoms of heart failure over some years. Presystolic murmur of mitral stenosis. Cardioscopy showed moderate cardiac enlargement, and pulmonary congestion. EC. shown in Fig. 6.

On one occasion arrhythmia converted into auricular fibrillation by digitalis therapy, but later neither digitalis nor quinidine prevented or relieved attacks. Death took place from heart failure and pulmonary infarction.

Case 6. A man, aged 68, with hypertensive heart failure. Increasing breathlessness for five months. Severe nocturnal dyspnoea for three months. Four attacks of palpitation in last ten days; last attack had been persisting for four days. Great cardiac enlargement and pulmonary congestion from hypertension. EC. shown in Fig. 7.

Quinidine for ten days had no effect on abnormal rhythm, but digitalis over same period slowed ventricular rate and established normal rhythm seven days later.

Case 7. A woman, aged 58, with mitral stenosis and hypertension. Dyspnoea for a year and attacks of tachycardia for a month. Blood pressure 220/115. Clinical signs of mitral stenosis. Cardioscopy showed moderate cardiac enlargement, and pulmonary congestion. EC. shown in Fig. 8.

Digitalis on one occasion changed rhythm to auricular fibrillation. Quinidine was never prescribed. Death came suddenly from pulmonary infarction.

Case 8. A woman, aged 65. Attacks of palpitation for 3 years. Systolic and mid-diastolic murmurs of mitral stenosis. Cardioscopy showed moderate enlargement of heart. EC. shown in Fig. 10.

Quinidine restored normal rhythm on one occasion, and digitalis converted it into auricular fibrillation another time.

Case 9. A woman, aged 53. Sudden onset of tachycardia eight days before. Clinical diagnosis obscured by tachycardia, but cardioscopy showed great enlargement of heart from mitral stenosis. EC. shown in Fig. 11.

Quinidine for 7 days had no effect, but digitalis converted it into auricular fibrillation.

Case 10. A man, aged 52. Frequent attacks of palpitation lasting an hour or a day at a time for eight years. Presystolic murmur of mitral stenosis. Cardioscopy showed moderate enlargement of heart, and slight pulmonary congestion. EC. shown in Fig. 12.

Neither quinidine nor digitalis prevented or aborted attacks.

Case 11. A woman, aged 63, with hypertensive heart failure. Symptoms and signs of left ventricular failure for some months with recent onset of attacks of paroxysmal tachycardia. Cardioscopy showed enlargement of left ventricle, and pulmonary congestion. EC. showed auricular tachycardia with 2:1 A-V dissociation; A.R., 292; alternate auricular waves within S wave.

Digitalis and quinidine had no effect on attacks.

Case 12. A man, aged 58, with mitral stenosis. Frequent short attacks of palpitation over many months. EC. shown in Fig. 9.

Quinidine was never given. Digitalis on one occasion changed rhythm to auricular fibrillation and thence to normal rhythm.

Case 13. An otherwise healthy woman, aged 38. Brief attacks of palpitation. No abnormal clinical findings in between attacks. EC. shown in Fig. 13.

Neither quinidine nor digitalis prevented or relieved attacks.

Case 14. An otherwise healthy woman, aged 34. Complained of attacks of palpitation, lasting a few minutes or hours, for 18 months. No abnormal signs on clinical examination which included cardioscopy. EC. shown in Fig. 14.

Neither quinidine nor digitalis was tested for relief or prevention of attacks.

Case 15. A woman, aged 61. Recent onset of heart failure from hypertension, and attacks of palpitation. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 332; alternate auricular waves within T wave.

Patient died soon after admission into hospital and before quinidine or digitalis could be tried.

Case 16. A man, aged 50. Symptoms of heart failure from mitral stenosis and aortic incompetence for one year with recent onset of attacks of palpitation. EC. shown in Fig. 21.

Patient died in hospital before effects of digitalis or quinidine could be observed.

Case 17. An otherwise healthy woman, aged 64. Complained of frequent attacks of tachycardia lasting for hours at a time and over a period of twelve years. No abnormal signs on clinical examination nor on cardioscopy. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 342; alternate auricular waves within S wave.

Neither digitalis nor quinidine proved effective as prophylactic measure.

Case 18. A man, aged 53. Recent cardiac infarction with fall of blood pressure to 90/70. Developed rapid heart action, and EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 364; alternate auricular waves within S wave. Inversion of T in leads II and III during normal rhythm, disappearing in subsequent tracings, was regarded as effect of tachycardia, but inversion of T I persisted as evidence of cardiac infarction.

Quinidine had no effect on tachycardia, but digitalis changed it into auricular fibrillation before converting it into normal rhythm.

Case 19. A man, aged 59, with hypertensive heart failure. Developed cardiac infarction and rapid heart action. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 376; alternate auricular waves within T wave.

Patient died before effects of digitalis or quinidine could be tested.

Case 20. An otherwise healthy woman, aged 19. Recurrent attacks of palpitation. No evidence of heart disease on clinical examination nor on cardioscopy. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 380; alternate auricular waves within S wave.

Attack aborted before quinidine or digitalis could be tried.

Case 21. An otherwise healthy woman, aged 50. Periodic attacks of palpitation for 16 years. No evidence of cardiovascular disease on clinical examination nor on cardioscopy. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 400; both auricular waves obscured by S and T waves.

Digitalis and quinidine ineffective in relieving or preventing attacks.

Case 22. An otherwise healthy man, aged 22. Four attacks of rapid heart action within six years. Attacks more frequent for three months. On clinical examination and cardioscopy no abnormal signs. EC. shown in Fig. 15.

Digitalis appeared to shorten one attack, and quinidine another.

Case 23. A man, aged 55, with tachycardia three weeks after cardiac infarction. EC. showed auricular tachycardia with 2:1 A-V dissociation; A.R., 400; both auricular waves obscured by S and T waves.

Attack persisted until death, 8 days later. Quinidine failed to change rhythm. Digitalis was not tried.

Case 24. An otherwise healthy man, aged 25. Periodic attacks of palpitation. Clinical and radiological examination showed no cardiovascular disease. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 422; both auricular waves obscured by S and T waves.

Neither quinidine nor digitalis was tried.

Case 25. A man, aged 54. Periodic attacks of palpitation over 20 years. Clinical and radiological evidence of mitral stenosis and aortic incompetence. EC. during attack showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 434; both auricular waves obscured by S and T waves.

Neither quinidine nor digitalis proved beneficial in preventing or relieving attacks.

Case 26. A woman, aged 42. Attacks of palpitation for two years. Cardioscopy showed moderate enlargement of heart from mitral stenosis, but there was no evidence of failure. EC. during an attack showed auricular tachycardia; auricular rate was 434 a minute one time and 218 another time, but with 2 : 1 A-V dissociation on both occasions.

Digitalis and quinidine were not tried.

Case 27. An otherwise healthy man, aged 42. Attacks of tachycardia, lasting upwards of 6 hours, for 5 years. Neither clinical nor radiological examination showed any cardiovascular disease. EC. shown in Fig. 16.

Both quinidine and digitalis failed to prevent or relieve attacks.

REFERENCES

- Barker, P. S., Wilson, F. N., Johnston, F. D., and Wishart, S. W. (1943). *Amer. Heart J.*, 25, 765.
 Barker, P. S., Wilson, F. N., and Johnston, F. D. (1943). *Ibid.*, 26, 435.
 Bourne, G. (1933). *Lancet*, 1, 686.

- Brown, W. H. (1936). *Amer. Heart J.*, 12, 307.
Campbell, M., and Elliott, G. A. (1939). *Brit. Heart J.*, 1, 123.
Campbell, M., and Suzman, S. S. (1934). *Lancet*, 2, 923.
Carr, F. B. (1932). *Amer. Heart J.*, 7, 668.
Decherd, G. M., Herrmann, G. R., and Schwab, E. H. (1943). *Ibid.*, 26, 446.
Dock, W. (1928). *Arch. intern. Med.*, 41, 745.
Evans, W. (1941). *Brit. Heart J.*, 3, 247.
Fine, M. J., and Miller, R. (1940). *Amer. Heart J.*, 20, 366.
Géraudel, E. (1937). *Arch. Mal. Cœur*, 30, 796.
Iliescu, C. C., and Sebastiani, A. (1923). *Heart*, 10, 223.
Jolly, W. A., and Ritchie, W. T. (1910). *Ibid.*, 2, 177.
Laubry, C., and Deglaude, L. (1932). *Arch. Mal. Cœur*, 25, 28.
Lewis, T. (1910a). *Heart*, 1, 98.
— (1910b). *Ibid.*, 1, 306.
— (1912). *Ibid.*, 3, 279.
— (1925). *The Mechanism and Graphic Registration of the Heart Beat*. Third ed., London.
— (1937). *Brit. med. J.*, 1, 1248.
Mackenzie, J. (1910). *Heart*, 2, 273.
MacWilliam, J. A. (1887). *J. Physiol.*, 8, 296.
Maddox, K. (1937). *Amer. Heart J.*, 14, 183.
Mines, G. R. (1913). *J. Physiol.*, 46, 349.
Orgain, E. S., Wolff, L., and White, P. D. (1936). *Arch. intern. Med.*, 57, 493.
Parkinson, J., and Bedford, D. E. (1927). *Quar. J. Med.*, 21, 21.
Parkinson, J., and Matthias, H. H. (1915). *Heart*, 6, 27.
Parkinson, J., and Nicholl, J. W. McK. (1922). *Lancet*, 2, 1267.
Parsons, C. G. (1943). *Brit. Heart J.*, 5, 187.
Sprague, H. B., and White, P. D. (1925). *Med. Clin. North Amer.*, 8, 1855.
Tanney, A. D., and Lilienfeld, A. (1942). *Ann. intern. Med.*, 16, 616.

CHEST LEADS FOR THE DEMONSTRATION OF AURICULAR ACTIVITY

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In certain forms of disorder of rhythm, the correct electrocardiographic diagnosis depends to a great extent on the proper demonstration and interpretation of the activity of the auricles. This is especially the case in paroxysmal tachycardia. However, it is often very difficult with the usual leads to identify the auricular wave and to ascertain its relation to the ventricular deflection, because it may be very small and obscured by the QRS complex or the T wave. Attempts have been made, therefore, to devise special leads in order to obtain large auricular deflections. In this respect, the œsophageal lead (Brown, 1936; Deglaude and Laubry, 1939) is undoubtedly the best method at present, but in view of the hardship it imposes on the patient it can only be used in selected cases and certainly not in routine clinical cardiography. The purpose of this paper is to assess the value of special chest leads employed in this department during the last year in a number of cases, which were under the care of Professor Hume, upon the assumption that they would show auricular waves to much better advantage than the routine leads. I first became interested in this problem in 1940 during my visits to the Cardiac Department of the London Hospital. Dr. William Evans showed me how clearly the auricular waves in various arrhythmias were demonstrated in chest leads and called my attention to this method of investigation.

Lewis (1910) was the first to use special chest leads to facilitate the study of auricular waves. He noticed in cases of auricular fibrillation that the auricular oscillations were maximal when the electrodes were placed over the right auricle. He pointed out that the chest leads as used by him were especially helpful in cases with an enlarged right auricle, for in these cases a larger area of the auricular wall was in apposition to the chest wall. Drury and Iliescu (1921) found that coarse auricular oscillations in auricular fibrillation were more continuously present in the chest leads than in the limb leads. They used two chest leads, sternal and antero-posterior, for the demonstration of auricular activity. In the sternal lead, one electrode at the junction of the second right rib with the sternum was paired with another over the seventh right costal cartilage; in the antero-posterior lead, one electrode was placed on the centre of the sternum, and the other on the back at the level of the inferior angle of the scapula, two inches to the right of the vertebral column. Holzman (1937) observed that the largest auricular deflections in the chest leads occurred when the exploring electrode was placed to the right of the sternum. Lian and Pinchenzon (1938) studied the auricular rhythm in the "precordial auricular lead S 5": in this lead, one electrode over the manubrium sterni was paired with another in the fifth right intercostal space. Schoenewald (1939) was able to obtain clearer P waves than those in lead II, by leading off from the right border of the sternum, at the level of the third intercostal space, to the right arm. Evans (1941) studied the auricular activity in lead CR₁ in 60 cases of auricular fibrillation, and showed that in many instances the auricular oscillations

were the most conspicuous in this lead. He failed to notice any close relationship between the size of the right auricle and the amplitude of the P waves. Williams and Ellis (1943) used special auricular precordial leads in their study of ventricular tachycardia: they placed the exploring electrode in the third intercostal space at the right sternal border, using first the right arm and then the left leg for the indifferent electrode; they stated that these leads have repeatedly clarified an otherwise doubtful diagnosis. Barker *et al.* (1943) suggested that in cases in which the P waves are small or indistinct in the standard leads, chest leads might prove helpful; in their opinion, by leading from two precordial contacts, one over the upper part of the sternum and the other over the ensiform process, it is usually possible to record large auricular waves.

METHOD AND MATERIAL

The method of taking special chest leads was that adopted by Schoenewald (1939), Faulkner (1943), and Williams and Ellis (1943). A circular electrode, 1.8 cm. in diameter, was used as exploring electrode and was placed in the third intercostal space at the right sternal border. The indifferent electrode was placed either on the right arm (to be referred to in this paper as auricular lead R) or on the left leg (auricular lead F). In several instances both leads were recorded. Except in a few cases, in the initial stage of our study, in which auricular lead F was recorded in reversed polarity for the sake of convenience, both auricular leads R and F and lead IV R were obtained in a manner corresponding closely to the recommendations of the Cardiac Society of Great Britain and Ireland and the American Heart Association (1939) i.e. the galvanometer connections were so arranged that relative positivity of the exploring electrode yielded an upward deflection on the finished curve. For the sake of conformity the few tracings originally recorded in reversed polarity and included in the analysis of this study have been reversed photographically. At first, auricular chest leads were recorded only in cases of paroxysmal tachycardia; but later their use was extended to other forms of arrhythmia and also to a number of cases showing sinus rhythm. Though the majority of the tracings showing sinus rhythm were in other respects abnormal and only a few normal cardiograms were available for comparative purposes, it was thought advantageous to include in this paper all available cases showing normal auricular rhythm.

PAROXYSMAL TACHYCARDIA

Ten cases were studied. In six, the auricular leads were regarded as helpful, in two cases they were of doubtful value, and in two cases they did not facilitate the reading of the tracings. In all six cases regarded as successful, there were clear P waves in at least one of the auricular leads; while the standard leads and lead IV R usually showed less distinct P waves. The cardiograms of these six cases are reproduced in Fig. 1-7. One of the two cases in which the auricular leads were considered to be of doubtful value was very probably ventricular tachycardia at a rate of 212 a minute. The ventricular complex was broad (0.12 sec.), and there was slurring near the base of the R wave in every second complex in the limb leads and in auricular lead F. The other case appeared to be auricular tachycardia at the rate of 180 a minute. The P waves seemed to be obscured by the T waves in all leads, but the configuration of the S-T segment and the T wave in both auricular leads R and F suggested the presence of a P wave much more strongly than did any of the standard leads. The two unsuccessful cases were thought to be auricular tachycardia. The P waves appeared to be obscured by the T waves and they were not identified with certainty in any of the recorded leads.

The cardiograms reproduced in Fig. 1 are those of a man, aged 63 years, who has had attacks of palpitation for the past four years. He was admitted to hospital for observation on July 7, 1943, and during his five weeks' stay he had several attacks which proved to

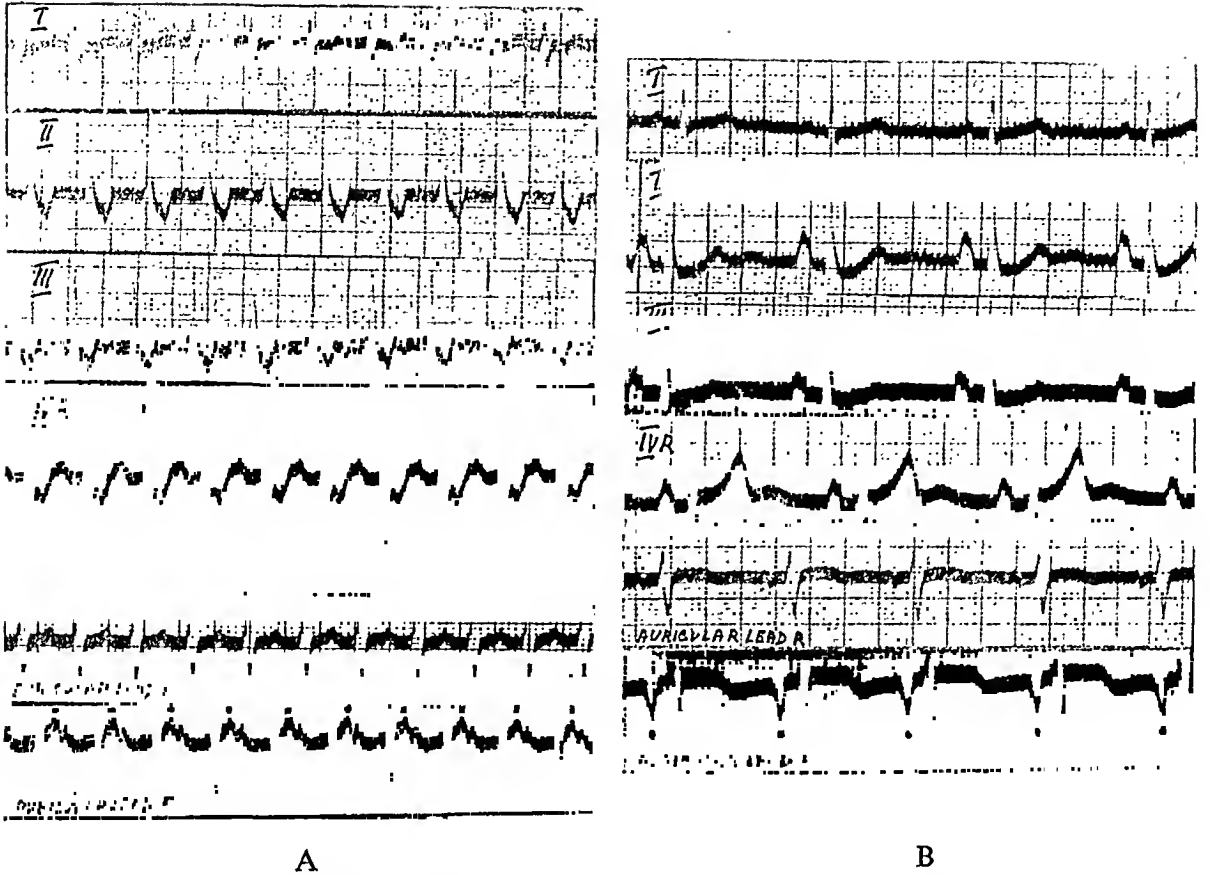


FIG. 1.—Case 1 (A). Nodal tachycardia at 176 a minute. Distinct P waves can be seen in auricular lead F. In this and subsequent figures dots denote the sites of the P waves in the auricular leads.
(B). Sinus rhythm. Note the large P waves in auricular lead F.

be paroxysms of supraventricular, probably nodal, tachycardia. No underlying structural disease was found in the heart. Fig. 1A shows such an attack at a rate of 176 a minute. There are no visible P waves in lead I. Though there is some suggestion of P waves in leads II and III, and also in IV R, auricular lead F is the lead in which P waves are most distinctly shown. Auricular lead R is similar to lead I and shows no clear P waves. Fig. 1B was taken a few days later after the tachycardia had stopped. It shows sinus rhythm with big P waves in lead II and in auricular lead F.

The cardiograms shown in Fig. 2 are those of a woman, aged 60 years, who had mitral stenosis and paroxysmal tachycardia. The first tracing shows auricular tachycardia at a rate of 166 a minute, with a 1 : 1 response. Auricular lead F appears to be the best lead for the demonstration of auricular activity. The second tracing, taken after digitalization, shows auricular tachycardia at the same rate as in the previous tracing, with a 2 : 1 A-V block. Here again, auricular lead F shows the most conspicuous P waves. Though the curves resemble auricular flutter, I decided eventually on paroxysmal tachycardia for the following reasons. (1) The rate (166 a minute) appeared to favour paroxysmal tachycardia. (2) The patient having been under observation for a long time before the tracings reproduced were taken had had numerous attacks of tachycardia, and in spite of practically continuous digitalization and massive doses of digitalis during some of the attacks, these attacks were apparently never converted into auricular fibrillation. Though clinically the rhythm was irregular at times and we thought it was auricular fibrillation, the available tracings showed distinct P waves at regular intervals with irregular ventricular activity, and unequal P-R intervals. The auricular deflections were separated by periods of electrical quiescence, thus making auricular flutter with variable block unlikely. I thought there were dropped beats or even A-V dissociation in one of the tracings. (3) Barker *et al.* (194)

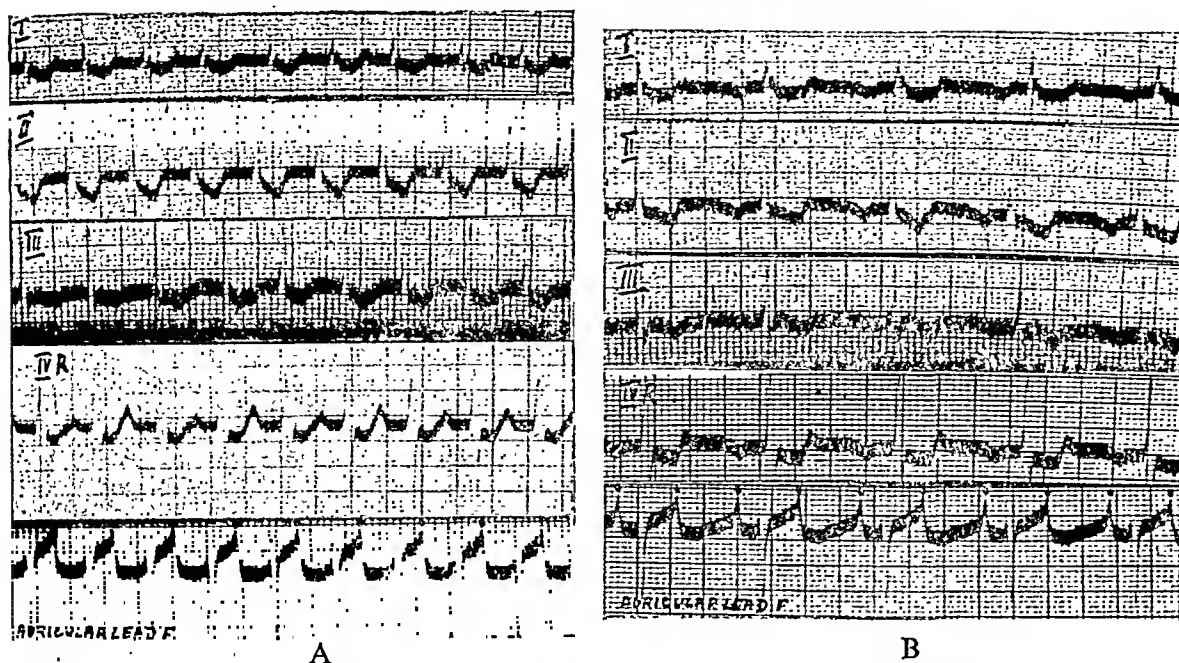


FIG. 2.—Case 2 (A). Probably auricular tachycardia with 1:1 response. Discussed in text. Rate 166 a minute. Clear, upright P waves in auricular lead F.
(B). Probably auricular tachycardia with 2:1 A-V block. Discussed in text. Note the large P waves in auricular lead F.

reproduced tracings which they interpreted as auricular tachycardia and some of them appeared very similar to my tracings—Barker's Fig. 2B, on page 773, interpreted as auricular tachycardia with a 1:1 response, and Fig. 2C, same page, following digitalis, as auricular tachycardia with 2:1 A-V block. Fig. 6A, on page 778, is strikingly similar to my Fig. 2B. Barker's Fig. 13A also shows similar features.

The curve shown in Fig. 3 was obtained from a R.A.F. pilot, aged 20 years, who was admitted to hospital in an attack of tachycardia.* A similar attack six months previously had lasted for three days. The heart was normal in size on radioscopy, and apart from the tachycardia no abnormality could be detected. The cardiogram shows a tachycardia with a ventricular rate of about 160 a minute. The QRS complex is slightly widened but not grossly aberrant. Leads I and III are not suitable for the analysis of auricular activity. Leads II and IV R suggest P waves at a rate lower than that of the ventricles. Clear inverted P waves can be identified in auricular lead F at a rate of 100 a minute, so that the diagnosis of ventricular tachycardia seems to be justified.

The patient whose cardiogram is reproduced in Fig. 4, was a woman, aged 64 years, who had high blood pressure and heart failure. In the first lead the rhythm is irregular and no P waves can be identified, simulating auricular fibrillation. In lead II, the ventricular complexes are slightly irregular in time, the rate varying from 134 to 166 a minute; here, there is definite evidence of regular auricular activity at a rate of about 158 a minute. Lead III is similar to lead I as regards rhythm. In lead IV R the ventricular rhythm is more or less regular, 158 a minute, and auricular waves cannot be identified with certainty. There is no clear evidence of auricular activity in auricular lead R. Auricular lead F shows clear, inverted P waves at slightly irregular intervals, at a rate of about 158 a minute. This is probably a case of paroxysmal tachycardia with auricular-ventricular dissociation, and with high auricular and ventricular rates.

The cardiogram shown in Fig. 5 is that of a man, aged 62 years, who was admitted to hospital in a desperate condition. The physical examination revealed a regular tachycardia. The patient died a few hours later, and autopsy showed a slight degree of coronary sclerosis,

* For this case I am indebted to Dr. George Davison.

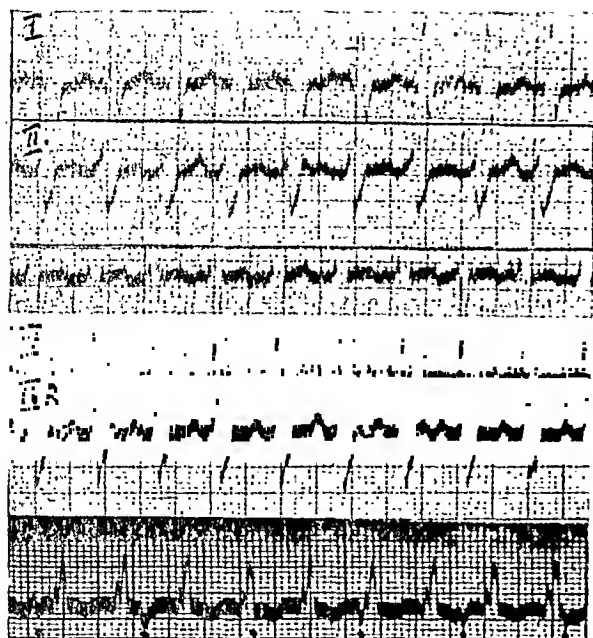


FIG. 3.—Case 3. Ventricular tachycardia. Ventricular rate 160 a minute, auricular rate 100 a minute. Clear, inverted P waves in auricular lead F.

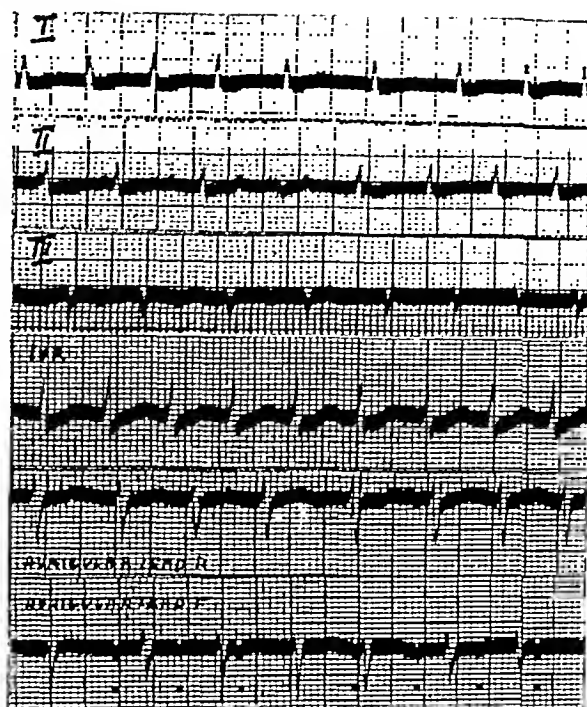


FIG. 4.—Case 4. A-V dissociation with high auricular and ventricular rates. Discussed in text. Distinct P waves are only seen in lead II and in auricular lead F.

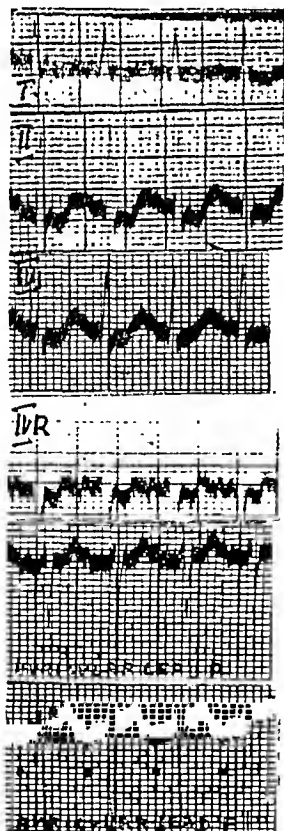


FIG. 5.—Case 5. Supraventricular tachycardia. Rate 170 a minute. Inverted P waves in auricular lead F.

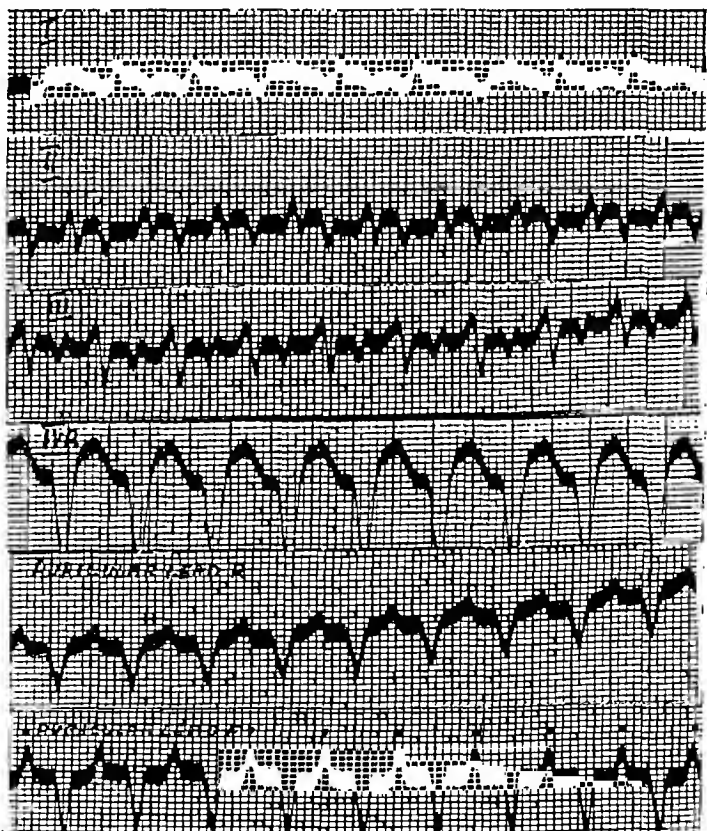


FIG. 6.—Case 6. Acute coronary artery occlusion. Tracing discussed in text. P waves are probably superimposed on T waves in auricular lead F. See also Fig. 7.

but no cardiac enlargement and no gross myocardial fibrosis; there were extensive pleural adhesions on the left side and partial collapse of the left lung. The patient was very restless, making it impossible to get a steady record. It shows supraventricular tachycardia. Though the tracing is technically unsatisfactory, auricular lead F shows the most distinct P waves. They are inverted, at a rate of about 170 a minute, and can be clearly differentiated from the preceding T waves. Auricular lead R shows diphasic P waves at the same rate.

The cardiograms shown in Fig. 6 and 7 are those of a man, aged 67 years, who was admitted with occlusion of the coronary artery and paroxysmal tachycardia. The tracings are diagnostic of anterior myocardial infarction. Fig. 6 shows probably auricular tachycardia at a rate of 160 a minute. The P waves in auricular lead F are, we think, superimposed on the T waves and probably this is the case in the other leads also. On the other hand, it is difficult to exclude flutter at the rate of 320 with a 2:1 response on this tracing alone. Fig. 7A, taken six days later after digitalization, shows auricular tachycardia at a rate of 150 a minute, with a 2:1 A-V block in the limb leads and Luciani-Wenckebach periods

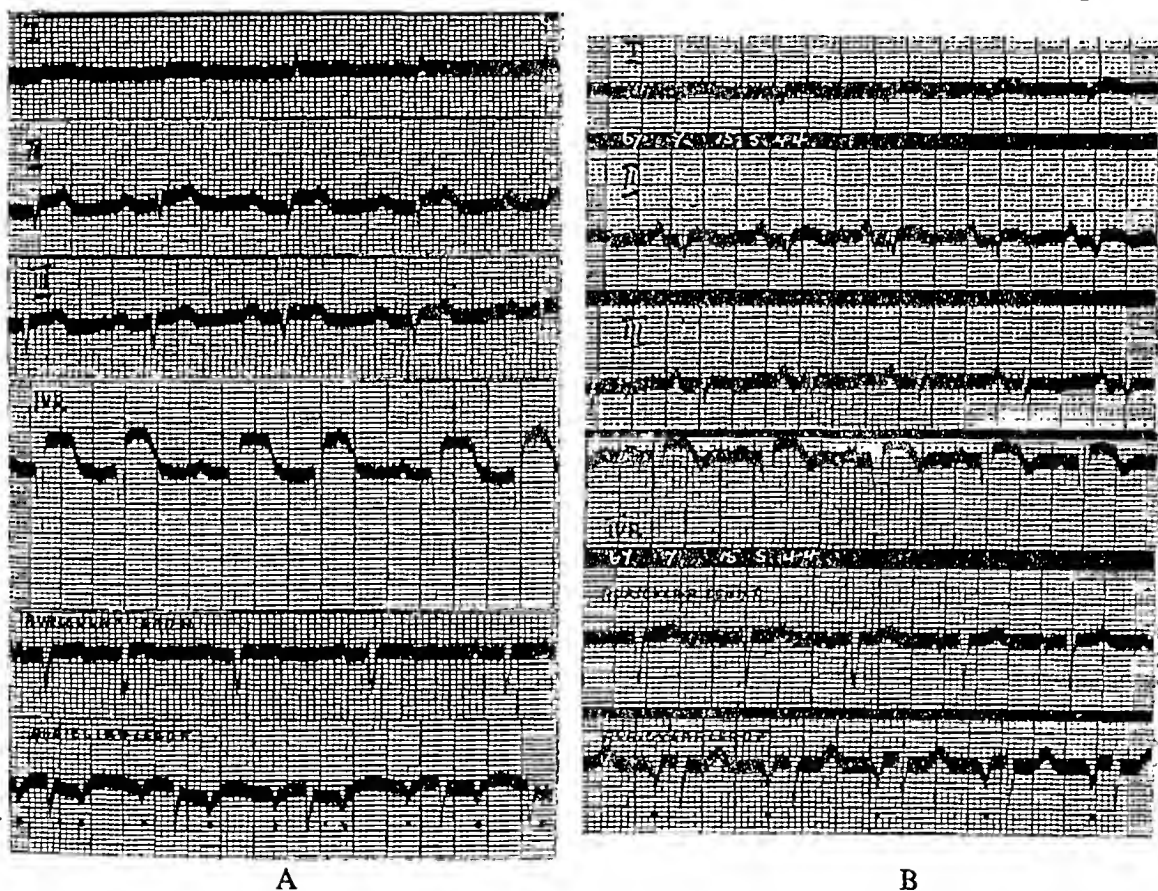


FIG. 7.—Case 6 (A). After digitalization. Auricular tachycardia at the rate of 150 a minute, with 2:1 A-V block in the limb leads and Luciani-Wenckebach periods at times in the chest leads. Inverted P waves in auricular lead F.
(B). After discontinuation of digitalis for 23 days. Sinus rhythm with normal P-R interval. Here again, inverted P waves in auricular lead F.

at times in the chest leads. Auricular lead F shows conspicuous inverted P waves. Fig. 7B, taken 23 days after discontinuation of digitalis, shows sinus rhythm with normal P-R interval, and auricular lead F shows deeply inverted P waves.

AURICULAR FLUTTER AND FIBRILLATION

Only one case of undoubted flutter was studied. The cardiogram of this patient, a man, aged 35 years, with mitral stenosis, is reproduced in Fig. 8 (page 245). It shows a 2:1 auricular flutter with marked flutter waves in auricular lead F.

Seven cases of auricular fibrillation were studied. In three of them the fibrillation waves were more conspicuous in the auricular leads than in the standard leads, while in the remaining four there was no appreciable difference.

SINUS RHYTHM

In addition to the cases of paroxysmal tachycardia in which tracings showing sinus rhythm were obtained after the paroxysm had stopped, 50 cases were available for study, and 60 cardiograms were taken. All but three were obtained from patients suffering from various forms of heart disease. It is not suggested that the auricular leads have any significant advantages over the standard leads in cases of normal auricular rhythm: nevertheless, a brief description of the form and amplitude of the P wave in the auricular leads may be of interest. Of the 60 cardiograms 15 included both auricular leads R and F. In the remaining 45 only auricular lead F was recorded. The P wave in auricular lead R was positive in 10, and diphasic in 5 instances. Only in one instance was the P wave in auricular lead R greater in amplitude than in auricular lead F; in another both leads showed equal P waves; and in 13 instances auricular lead F showed more conspicuous P waves than auricular lead R. A comparison of auricular lead R with the standard leads revealed only one case in which the largest P waves occurred in auricular lead R. In the remainder, at least one of the standard leads showed P waves either equal in amplitude to those in auricular lead R or even larger. The P wave in auricular lead F was upright in 3, diphasic in 6, and inverted in 51 instances. Auricular lead F was compared with the standard lead showing the largest P wave; and it was found that, judged by the amplitude of this wave, auricular lead F was superior to the standard lead in 19, equal to it in 16, and inferior in 25 instances.

DISCUSSION

The special chest leads used in this study often display larger auricular waves than the standard leads, and thus help the interpretation of records showing abnormal rhythms. Auricular lead F appears to be superior to auricular lead R. Though Wood and Selzer (1939) stated that the right arm was the better distal electrode for the study of auricular activity, it is open to question whether their results can be directly compared with ours because they used a different technique, placing the exploring electrode in the fourth intercostal space at the right sternal border (leads CR₁ and CF₁). In ten unselected cases we studied the P waves in both auricular leads R and F, and in leads CR₁ and CF₁; the comparative figures are shown in Table I. The amplitude of the P wave was measured in the four leads to the nearest 0.5 mm. from the top of the isoelectric line in upright waves and from the bottom in inverted waves. Though the number of cases is far too small to draw conclusions, it appears that auricular lead F is not only superior to auricular lead R, but is also the best of the four leads for the study.

TABLE I.—SIZE OF P WAVES IN VARIOUS LEADS

| Case Number | Rhythm | Amplitude of P wave in mm. in | | | |
|-------------|--------------------------------|-------------------------------|---------------|-----------------|-----------------|
| | | Auric. lead R | Auric. lead F | CR ₁ | CF ₁ |
| 1 (Fig. 8) | Auricular flutter | 1.5 | 3 | 1.5 | 2 |
| 2 | 2:1 A-V block | 2.5 | 2.5 | 2.5 | 2.5 |
| 3 | Sinus rhythm | 1 | 2 | 1 | 2 |
| 4 | Auricular fibrillation | 1 | 2 | 1 | 1.5 |
| 5 | Sinus rhythm | 2.5 | 1 | 2 | 1 |
| 6 | Sinus rhythm | 2 | 2.5 | 2 | 2.5 |
| 7 | Auricular fibrillation | 1 | 2 | 1 | 2 |
| 8 (Fig. 9) | Sinus rhythm | 1.5 | 4 | 4 | 2 |
| 9 | Auricular fibrillation | 1 | 1 | 1 | 1 |
| 10 | Sinus rhythm | 1 | 1 | 2 | 1 |
| | Mean amplitude | 1.5 | 2.1 | 1.8 | 1.75 |

of auricular activity. On the other hand, if the exploring electrode is placed in the fourth intercostal space at the right sternal border, the results are likely to be better when the exploring electrode is paired with the right arm than when paired with the left leg. An illustrative example is shown in Fig. 9. The cardiogram was obtained from a man aged 45 years, suffering

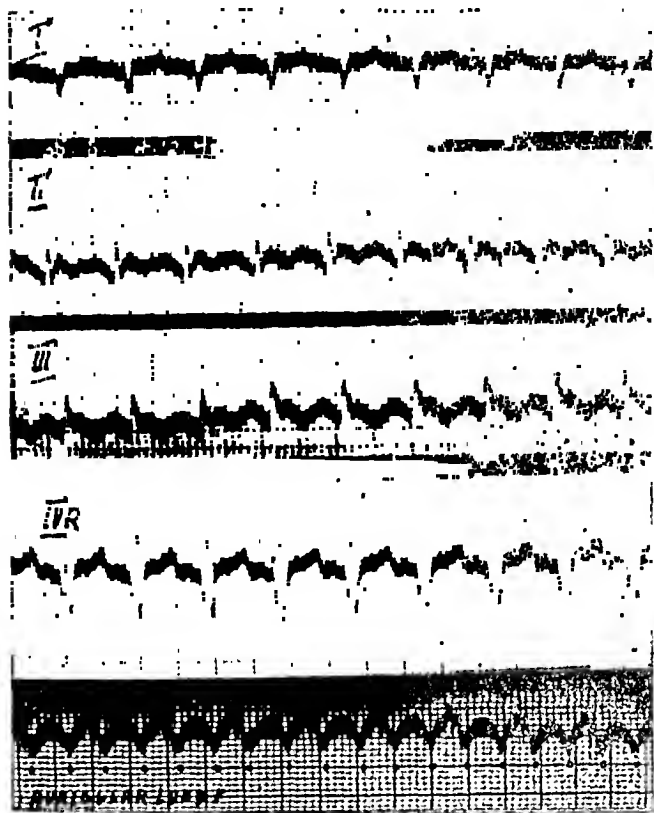


FIG. 8.—Case 7. Mitral stenosis, with 2 : 1 auricular flutter. Conspicuous flutter waves in auricular lead F.

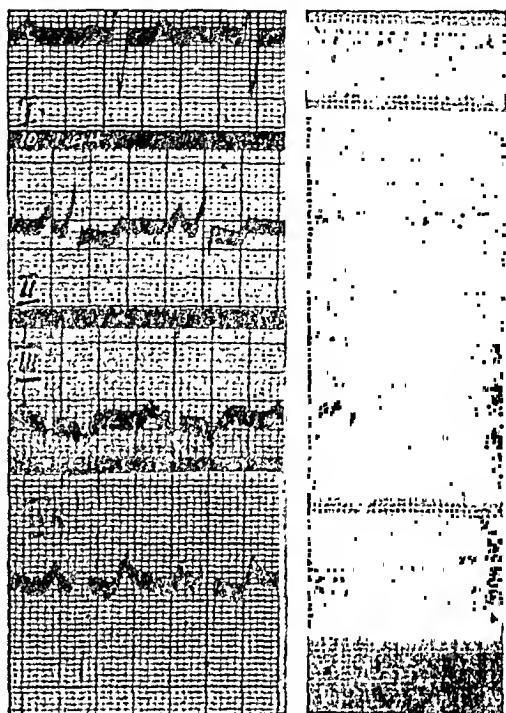


FIG. 9.—Case 8. Chronic cor pulmonale. Large auricular deflections in auricular lead F, and in lead CR₁.

from chronic cor pulmonale. The tracing shows equally large P waves in auricular lead F and in lead CR₁ (inverted in the former, upright in the latter), and much smaller P waves in auricular lead R and in lead CF₁. Another advantage of auricular lead F over lead CR₁ is that the P wave in the former is nearly invariably opposite in direction to that in lead II. Thus, a combined analysis of these two leads is more likely than any of the standard leads to disclose a P wave obscured by the ventricular complex, and especially by the T wave, combining to simulate a split T wave. The practical value of this can be seen in the tracings reproduced in Fig. 1A and 5.

In many records the auricular leads failed to display larger P waves than did the standard leads. It is not easy to explain this lack of uniformity. It would seem at first that the size of the right auricle is an important factor determining the amplitude of the P wave. Lewis (1910), in fact, found that the maximal oscillations occurred in cases of auricular fibrillation in which the right auricle was enlarged. On the other hand, Evans (1941) found that conspicuous auricular waves in lead CR₁ were by no means dependent on extension of the heart to the right. Our results agree with those of Evans. We were unable to find any close correlation between the size of the right auricle and the amplitude of the P waves in the auricular leads. Out of the six cases of paroxysmal tachycardia with distinct P waves in the auricular leads, four were examined radioscopically: in none was the right auricle seen to be enlarged; in two all cardiac chambers were normal in size; the third (coronary thrombosis) had moderate enlargement of the left ventricle; and the fourth (mitral stenosis) showed slight enlargement

of both ventricles and of the left auricle. The fifth case of paroxysmal tachycardia was too ill to be taken to the screening room; he died shortly after admission, and the autopsy revealed no cardiac enlargement. In the sixth case, there were no data available regarding the size of the heart apart from physical examination, which did not suggest cardiac enlargement. The four remaining cases of paroxysmal tachycardia with doubtful or unsuccessful auricular leads also had normal-sized right auricles: in one the heart was normal in size; in two there was slight enlargement of the left ventricle; in the fourth, which was not screened, autopsy showed only slight enlargement of the left ventricle. The patient with mitral stenosis and auricular flutter, whose cardiogram is reproduced in Fig. 8, was proved by radioscopy to have a general cardiac enlargement, including possible dilatation of the right auricle. In the cases of auricular fibrillation and sinus rhythm there was also a lack of correlation between the amplitude of the P wave and the size of the right auricle. It is noteworthy that in a case of mitral stenosis and auricular fibrillation with very marked enlargement of both auricles, confirmed by autopsy, the oscillations were hardly visible. On the other hand, a comparatively large P wave (3 mm. in amplitude) was encountered in a case of coronary thrombosis (T III type) in which the autopsy showed no auricular enlargement at all. It is evident from this analysis that the size of the right auricle cannot be the only factor determining the amplitude of the P wave. The anatomical position of the right auricle in the thoracic cavity and its relation to the anterior chest wall are possibly important factors influencing the amplitude of the P wave in the auricular leads; but at present we have no confirmatory evidence in support of this suggestion.

SUMMARY

Special chest leads were used for the study of auricular activity and compared with the standard leads. The exploring electrode was placed in the third intercostal space at the right sternal border and paired with the right arm or left leg. The former lead was referred to as auricular lead R, the latter as auricular lead F. Auricular lead F was found to be more useful than auricular lead R.

These special chest leads were studied in cases with paroxysmal tachycardia, with auricular fibrillation and flutter, and in a number with sinus rhythm. They showed auricular waves often to much better advantage than did the standard leads. It is suggested, therefore, that the recording of these leads is indicated in all cases in which there is doubt about the activity of the auricles.

No correlation was found between the size of the right auricle and the amplitude of the P wave as recorded in the auricular leads. It seems, therefore, that the amplitude of the P wave in the auricular leads is also determined by factors other than the size of the right auricle. The anatomical position of the right auricle in the thoracic cavity and its relation to the anterior chest wall are suggested as possible factors.

I am indebted to Professor Hume for his helpful criticism and advice. I wish to thank Dr. Maurice Campbell and Dr. William Evans for their suggestions, and Dr. I. E. McCracken, Medical Officer of Health, Newcastle on Tyne, and Dr. G. P. Harlan, Medical Superintendent, Newcastle General Hospital, for facilities provided.

REFERENCES

- Barker, P. S., Wilson, F. N., Johnston, F. D., and Wishart, S. W. (1943). *Amer. Heart J.*, 25, 765.
 Brown, W. H. (1936). *Ibid.*, 12, 307.
 Deglaude, L., and Laubry, P. (1939). *Arch. Mal. Cœur*, 32, 121.
 Drury, A. N., and Iliescu, C. C. (1928). *Heart*, 8, 171.
 Evans, W. (1941). *Brit. Heart J.*, 3, 247.
 Faulkner, J. M. (1943). Quoted by Williams and Ellis.
 Holzman, M. (1937). *Arch. f. Kreislauff.*, 1, 1.
 Lewis, T. (1910). *Heart*, 1, 306.
 Lian, C., and Pinchenzon, B. (1938). *Cardiologia*, 2, 56.
 Schoenewald, G. (1939). *Middl. Hosp. J.*, 39, 183.
Standardization of Precordial Leads. Memorandum by the Cardiac Society of Great Britain and Ireland and the American Heart Association (1939). *Brit. Heart J.*, 1, 43.
 Williams, C., and Ellis, L. B. (1943). *Arch. intern. Med.*, 71, 137.
 Wood, P., and Selzer, A. (1939). *Brit. Heart J.*, 1, 49.

PROCEEDINGS OF THE CARDIAC SOCIETY OF GREAT BRITAIN AND IRELAND

The EIGHTH ANNUAL GENERAL MEETING of the Cardiac Society of Great Britain and Ireland was arranged to be held at University College Hospital Medical School, London, on Thursday, July 20, 1944, under the Chairmanship of SIR THOMAS LEWIS, F.R.S.

Early in July a majority of the Council decided reluctantly that this meeting should not be held.

PRIVATE BUSINESS

The following private business was conducted by postal vote with the written approval of 23 ordinary members, no members objecting.

1. The minutes of the last meeting were printed in the Journal (5, 238, 1943).
2. The accounts, held over for audit and approval, showed a balance of £40 7s. 5d. The Council had decided that no subscription should be collected for the year 1944/45.
3. The Secretary, on the recommendation of the Council, was re-appointed for another year and William Evans was again asked to act as Assistant Secretary.
4. Four Ordinary Members were elected as *Extra-Ordinary Members*.

A. G. Gibson
Donald Hall

W. E. Hume
H. J. Starling

5. The following new Members were elected:—

Ordinary Members
Janet Aitken
Doris Baker

Associate Members
D. R. Cameron
J. R. B. Hern

Six Associate Members were re-elected for another period of three years.

6. Subsequently, by postal vote, A. A. F. Peel, Glasgow, and B. T. Parsons-Smith, London, were elected members of the Council for the years 1944–48.
7. The Secretary reports the following events and decisions of the Council as he was unable to bring them before the Meeting.

- (a) He had written on behalf of the Society to the relatives of Frederick John Poynton, Honorary Member, whose obituary notice had been published in the Journal (6, 96, 1944).
- (b) In accordance with the decision of the last General Meeting, the Secretary had approached the British Pædiatric Association, who had agreed that their Committee and the Committee of the Cardiac Society should meet together to try and draw up a combined report on The Care of Rheumatic Children. The draft report was produced later in the year and certain modifications were made in this by the Executive of the B.P.A. The Council of the Cardiac Society at its meeting on March 22, 1944, discussed this report and asked the Chairman, Sir Maurice Cassidy, and the Secretary, Maurice Campbell, to accept the invitation to attend the meeting of the Executive of the British Pædiatric Association, with authority to propose and accept minor changes within certain limits discussed by the Council. The Chairman and Secretary attended this meeting on March 25, 1944, and agreement was reached to publish the document as a joint report by the Cardiac Society and the British Pædiatric Association. *British Heart Journal* (1944), 6, 99.
- (c) The Royal College of Physicians had asked the Cardiac Society to appoint a member to serve on the Committee for the revision of the Nomenclature of Diseases and the Council had appointed Maurice Campbell. Subsequently the R.C.P. Committee asked the Cardiac Society to appoint two members to help with the revision of the

PROCEEDINGS OF THE CARDIAC SOCIETY OF

section on Diseases of the Circulatory System, and the Secretary with the approval of the Chairman submitted the names of John Parkinson and Maurice Campbell.

- (d) The Memorandum on Rehabilitation of Cardiac Patients was further considered by the Council, and with further modifications was approved for publication at the Council Meeting on March 22, 1944. The Secretary was instructed to send it for publication to the *British Medical Journal* (April 22, 1944) and to the *Lancet*. It is reprinted below.

PUBLIC BUSINESS

The proposed programme of Public Business was as follows:—

DISCUSSION

DISEASES OF THE PERICARDIUM

Opened by TERENCE EAST; BRUCE PERRY, JOHN PARKINSON, and TUDOR EDWARDS

DEMONSTRATIONS

SPECIMENS OF NORMAL AND PATHOLOGICAL A-V CONDUCTION

SIR THOMAS LEWIS

A CASE OF AORTIC ANEURYSM, SUCCESSFULLY WIRED

GEOFFREY BOURNE

SHORT COMMUNICATIONS

A CASE OF TUBERCULOUS PERICARDITIS

LESLIE COLE

(Published in full; p. 185)

THE ACTION OF INTRAVENOUS DIGOXIN

J. McMICAL and E. V. SHARPEY-SCHAFER

ELECTROCARDIOGRAMS OF A DYING HEART AFTER CORONARY THROMBOSIS

T. F. COTTON

CARDIAC ENLARGEMENT WITH BRADYCARDIA IN RECRUITS

CRIGHTON BRAMWELL

CARDIAC ENLARGEMENT IN ANÆMIA

ALASTAIR HUNTER

THE NATURE OF PAROXYSMAL TACHYCARDIA

WILLIAM EVANS

(Published in full; p. 221)

SURGICAL TREATMENT OF PATENT DUCTUS ARTERIOSUS

RAE GILCHRIST

(To be published in full; 7, p. 1, 1945)

TWO CASES OF MALIGNANT HYPERTENSION TREATED BY UNILATERAL NEPHRECTOMY

C. BRUCE PERRY

NOMENCLATURE OF CARDIAC DISEASE

MAURICE CAMPBELL

REHABILITATION OF CARDIAC PATIENTS

Many patients, those with fractures, for example, derive great help from efficient rehabilitation. Without it they may be handicapped for long periods; with it most of them may be enabled to undertake full activities and to resume their normal work. The success achieved in this direction has led to the suggestion that similar methods should be used more widely, and the Council of the Cardiac Society felt the time was opportune for expressing their views and bringing forward some questions for wider discussion.

Patients with heart disease are in rather a special category as regards rehabilitation. In the first place any activity, including walking or other forms of physical effort, must automatically increase the work done by the heart. If the patient is going to recover completely, e.g. after some temporary infection, cardiac recovery will often proceed *pari passu* with recovery from the infection and no more than simple graduated exercises may be needed to ensure it; in fact he may need limiting rather than encouraging in his rate of progress. In other cases complete recovery may be impossible, and it may be most important that he should not return to his previous work and activity.

Further, the correct diagnosis of the condition of the heart and especially of the heart muscle, and the correct assessment of the cardiac reserve are of fundamental importance, and harm may be done by too much or by too little activity at any particular stage.

In our opinion there is only limited scope for rehabilitation, as the term is now being employed, for patients suffering from organic cardiovascular disease. Physiotherapy and graduated exercise are, of course, useful, but must be supervised by a doctor with special knowledge of heart disease. The main problem is the decision as to how much general activity should be allowed, and this depends more on the success of the doctor in charge in diagnosis and assessment of the patient's cardiac reserve than on the availability of skilled assistants in physiotherapy or occupational therapy. The need for suitable convalescent homes is, of course, generally accepted.

There are, however, cases in which the heart is temporarily under suspicion, which fuller investigation proves to be unjustified, e.g. systolic murmurs which the inexperienced may hesitate to disregard but the experienced are able to label as "insignificant." In many such cases all that is necessary is for an authoritative opinion that the heart is normal and that the patient is, therefore, capable of leading a full active life, but in others rehabilitation may be needed. There is also scope for rehabilitation in the case of effort syndrome, which is at least as common in civil life as under service conditions, though here it may appear diagnosed as "cardiac anxiety state," "traumatic neurasthenia" or "post-influenzal tachycardia." But we suggest that the rehabilitation of these patients, whether by graduated exercises or by simple psychotherapy, should not be carried out at cardiac clinics, once it has been decided that there is no organic disease.

We suggest, therefore, that there should be more well-staffed and well-equipped out-patient cardiac clinics at general hospitals, preferably under the care of an experienced cardiologist. Here a correct diagnosis could be made, and the patient could be advised about suitable employment and be kept under observation when engaged in such employment. The help of the Almoner's department would often be useful. If necessary the patients could receive specialized treatment that experience has shown to be more satisfactory in cardiac clinics, such as the treatment of auricular fibrillation with digitalis or of congestive failure with mercurial diuretics, or the control of symptoms of early angina.

Special difficulties may arise in finding suitable work for patients with some permanent limitation as a result of heart disease, and this is a problem that should be discussed. Many such persons, especially the younger ones with rheumatic heart disease, are precluded from those occupations which are most appropriate to their condition, e.g. Civil Service, Banking, and Insurance. They are, therefore, forced to take less suitable work for which no medical examination is necessary and in which their health may break down. Alternatively, they are out of employment and the nation is losing citizens who might give valuable service for a considerable number of years.

We recommend that where a patient is fit for particular work his acceptance should not be impossible because he has valvular disease which precludes his joining an ordinary life assurance scheme; it should be possible to make special arrangements for accepting such patients in some branches of the Civil Service, Banking, etc.

Another difficulty is with the older patient who is beginning to be incapacitated by early signs of failure or angina or by such lesions as hypertension, arteriosclerosis, or myocardial disease which may lead to failure if his previous employment is no longer suitable. Such a patient would often be

better at work and would like to be at work, but cannot find anything because he is not fit for the heavy work that he did before.

We recommend that there should be some industrial advisory board or government department, through which arrangements could be made to ensure that these partially disabled patients could obtain suitable work, after, when necessary, appropriate special training. Often this would not be necessary and the patients' previous employers might be able to carry out the medical recommendations, especially if they were safeguarded against claims against them under the Employers' Liability Act,* in the event of a breakdown of an employee known to be suffering from heart disease.

The special care of rheumatic children is being dealt with elsewhere in a separate memorandum.

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MAURICE CAMPBELL;

Secretary.

Cardiac Society of Great Britain and Ireland.

* It has been pointed out that the Workman's Compensation Act should be referred to here.

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